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1-Benzyl isoquinolines: Studies in their synthesis, cyclisation and migration.

White, Anthony William Charles

Award date:
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1-BENZYL ISOQUINOLINES: STUDIES IN THEIR
SYNTHESIS, CYCLISATION AND MIGRATION

submitted by

ANTHONY WILLIAM CHARLES WHITE

for the degree of Doctor of Philosophy

of the University of Bath

1975

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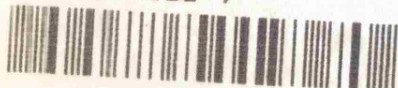


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ACKNOWLEDGEMENTS

I would like to express my thanks to my Supervisor Dr. S.F. Dyke for his constant interest and advice during the course of my research.

Allen and Hanburys' Ltd. is also gratefully acknowledged for the financial support for this work.

The technical staff of the School of Chemistry, and fellow postgraduate students at the University of Bath are gratefully thanked for their companionship and assistance; in particular Mr. R.I.M. Brown for the mass spectra, Dr. D.W. Wiggins and Mr. D. Woods for some N.M.R. data and Dr. R.G. Kinsman for his valuable advice concerning Chapter 3 of this thesis.

Thanks are also due to Dr. D.W. Brown for critically reading part of the thesis in draft form after Dr. Dyke's departure on sabbatical leave (June 1973).

PREFACE

The research described in this thesis was carried out at the University of Bath between October 1970 and October 1973.

I.R. spectra were determined on a Perkin-Elmer 237 Spectrophotometer as nujol mulls unless otherwise stated, and ν_{\max} is expressed in cm^{-1} . U.V. spectra were determined on a Perkin Elmer 137 spectrophotometer in 95% ethanol, unless otherwise stated, λ_{\max} is expressed in nm. N.M.R. spectra were obtained using a Varian A-60 spectrometer or a J.E.O.L. P.S 100, and chemical shifts are expressed in ppm downfield from T.M.S. as internal standard. Mass spectra were measured on an A.E.I. MS 12 spectrometer and relative peak intensities are quoted as a percentage of the base peak. All melting points are uncorrected.

SUMMARY

Chapter 1 of this thesis contains a brief review of the structure-activity relationships in bronchodilator drugs, and describes the syntheses of 5-hydroxy and 7-hydroxy-6-hydroxymethyl-1(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolines as potentially active compounds. The preliminary pharmacology of these saligenins are also included. The synthesis involves a Pomeranz-Fritsch type of cyclisation which occurs in an abnormally high yield with the additional anomaly of a high ortho/para ratio. Introduction of the 1-benzyl substituent was achieved by use of the Reissert reaction, and involves a novel, high yield method for decomposition of the 1-benzyl-2-benzoylisoquinaldonitrile to the 1-benzyl aromatic isoquinoline. An interesting tetracyclic compound is described which arises from acid treatment of the isoquinaldonitrile, and prompted the investigation of isopavine alkaloids discussed in Chapter 2.

The two possible isomeric structures for the alkaloid reframoline are synthesised by a novel route involving aminonitrile intermediates. Professor J. Slavik showed that only one of the prepared isopavines was identical by thin layer chromatographic properties and infrared spectrum with the naturally occurring alkaloid reframoline. A significant difference was observed in the U.V. spectra in alkaline solution, of the two methine bases prepared by Hofmann degradations.

From the same isopavine syntheses the two related pavines were prepared, one of which confirmed the structure of the alkaloid caryachine as 2,3-methylenedioxy-8-hydroxy-9-methoxypavinane. Nor-caryachine was also prepared and identified with caryachine by N-demethylation and N-methylation reactions. Apart from pavine itself, nor-caryachine is the only N-H pavine known.

Among some interesting side reactions observed in the above work was an example of the known $C_1 \rightarrow C_3$ benzyl migration via the 1-benzyl-1,2-dihydroisoquinoline intermediate. This reaction is believed to be a concerted bimolecular exchange reaction, and work described in Chapter 3 confirms this by crossed migration reactions of 1,2-dihydroisoquinolines, both chiral at C_1 and racemic. Two possible transition states for the reaction have been advanced prior to this work, one of which involves two molecules of the same configuration at C_1 and the other, two molecules of opposite configuration. The distribution of products of various migration reactions, as shown by T.L.C. and mass spectrometry, can only be explained by the involvement of both transition states.

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DISCUSSION

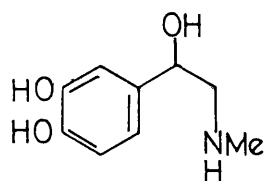
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CHAPTER 1 : INTRODUCTION1. Structure - activity relationship in β -adrenoreceptor stimulants.^{1,2}

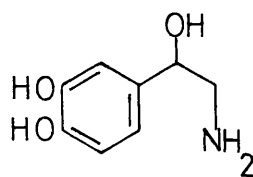
Difficulty in breathing due to bronchospasm occurs most commonly in bronchial asthma. Bronchospasm is an involuntary contraction of the bronchiolar smooth muscle and is often accompanied by swelling of the respiratory tracts' mucosa. It is caused by an allergic response from sensitisation to foreign proteins or antigens which promote antibody formation. Circulation of the antibodies in the blood stream and further exposure of the host to the same antigen result in an allergic response which is accompanied by the release of spasmogens eg. histamine and 5-hydroxytryptamine. Such spasmogens cause vasodilation, bronchoconstriction and increased secretion by the tear glands and respiratory passages; the latter effects increase difficulties in breathing by obstruction of the bronchioles. Asthma is effectively treated with bronchodilator drugs which stimulate β -adrenoreceptors by acting as sympathomimetics to produce relaxation of bronchiolar smooth muscle which allows easier passage of air in and out of the lungs.

Ahlquist³ compared the action of a number of sympathomimetics including the catecholamines adrenaline (1), noradrenaline (2) and isoprenaline (3), on smooth muscle. He found that in smooth muscle, which responds to the drugs' action by

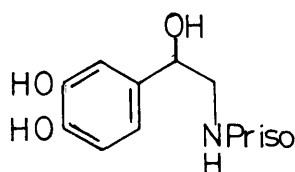
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(1)



(2)



(3)

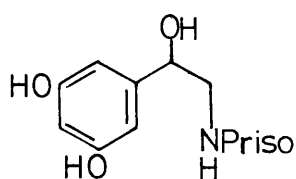
contraction, the order of potency of the catecholamines is adrenaline > noradrenaline > isoprenaline, but where response to the drug is by way of relaxation the order of potency is reversed. He explained this by postulating two types of receptor, α and β . Cells with α -receptors have a high sensitivity to adrenaline (1) and noradrenaline (2) but a low sensitivity to isoprenaline (3), whereas β -receptors have a high sensitivity to isoprenaline but lower sensitivity to adrenaline and noradrenaline.

The direction of response of an organ to a drug will depend on three main factors:

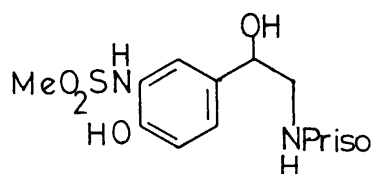
- (a) The presence of one or other of the receptor types, or if both α and β are present, which receptor predominates.
- (b) The affinity of the activating substance for the two types of receptor.

- (c) The type of smooth muscle present in the organ, ie. does it respond with relaxation or contraction?

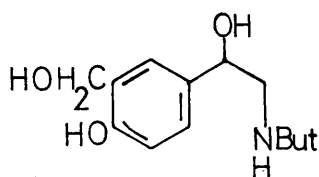
From Ahlquist's work it follows that as the N-alkyl substituent of the catecholamine is made more bulky, β -receptor agonism is increased; thus isoprenaline (3) is potent at β -receptors but virtually inactive at α -sites. Each of the functional groups of isoprenaline contributes towards the activation of the β -receptor, and almost any change in structure, other than N-substitution, lowers the potency. However, attempts to alter the catechol moiety of isoprenaline (3) have furnished other active compounds eg. orciprenaline (4), soterenol (5)⁴ and salbutamol (6)^{5a,b}. A different approach



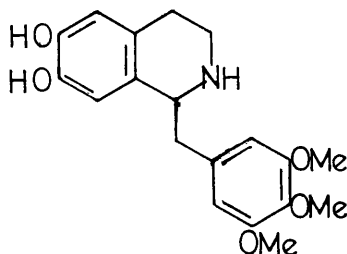
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(5)



(6)

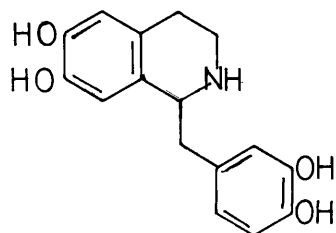


(7)

gave trimetoquinol (7)⁶ which is, in effect, a cyclised catecholamine with potent β -receptor agonist activity, despite the absence of a β -hydroxy group.

The saligenins as β -receptor agonists are less potent than catecholamines but have a much more selective action. The heart and bronchioles both contain β -receptors, salbutamol (6) acts on bronchiolar β -receptors, but has little or no effect on the β -receptors of the heart. This has led to the idea of two possible types of β -receptor, β_1 and β_2 ; hence if salbutamol has a greater affinity for say β_2 - receptors and these predominate in bronchiolar tissue, but not in cardiac tissue, this would explain the more selective action of salbutamol on bronchiolar smooth muscle. In addition to the selective action of salbutamol (6), it is more stable in the body than is isoprenaline (3), less easily removed from sites of action, and has a longer duration of action^{5a,b}. The hydroxy group para substituted with respect to the side chain is essential for activity, as also is the alcoholic hydroxymethyl hydrogen atom.

Of the cyclised catecholamines, 1,2,3,4-tetrahydro-papaveroline (8) was shown⁸ to be a moderately potent β -receptor agonist; but of some sixty related 1-benzyl-1,2,3,4-tetrahydroisoquinolines tested, trimetoquinol (7) was by far the most active. This poses new problems in an explanation of structure-activity relationships for β -receptor agonists.^{9a,b,c}

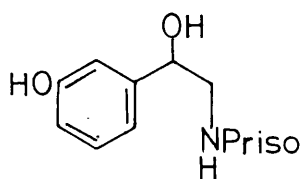


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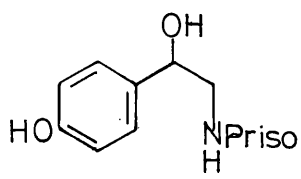
Recent Theories.

Several theories have been forwarded, notably those by Larzen et al,^{10a,b} to explain β -adrenergic actions and such observations as:

- (a) The meta monophenolic analogue (9) of isoprenaline (3) is about five times as active as the para isomer (10); and orciprenaline (4), which contains two meta phenolic functions is very active.

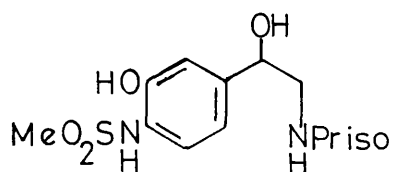


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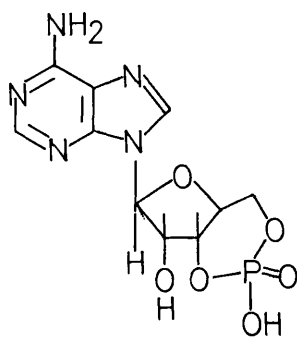
(10)

(b) Soteranol (5) is much more potent than its reversed isomer (11).

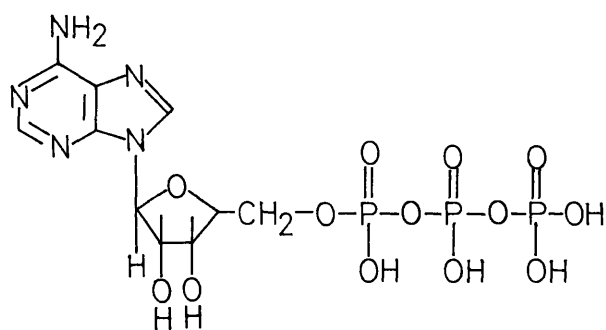


(11)

Such simple theories, however, have given way to a more satisfactory explanation of β -adrenergic action^{2,12a,b} which is concerned with the long known fact that β -agonistic catecholamines enhance the rate of formation of 3',5'-cyclic adenosine monophosphate (cyclic AMP) (12), from adenosine triphosphate (ATP) (13), in the presence of the enzyme "adenyl cyclase". This effect is inhibited by β -receptor



(12)



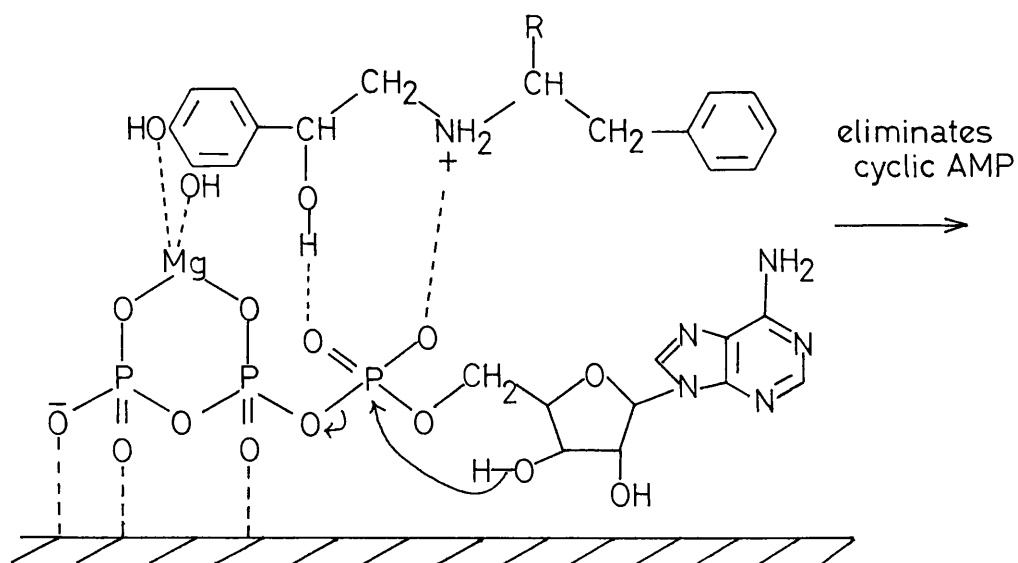
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blocking agents, (termed β -blockers, which are substances which adsorb strongly to the β -receptor sites but have not

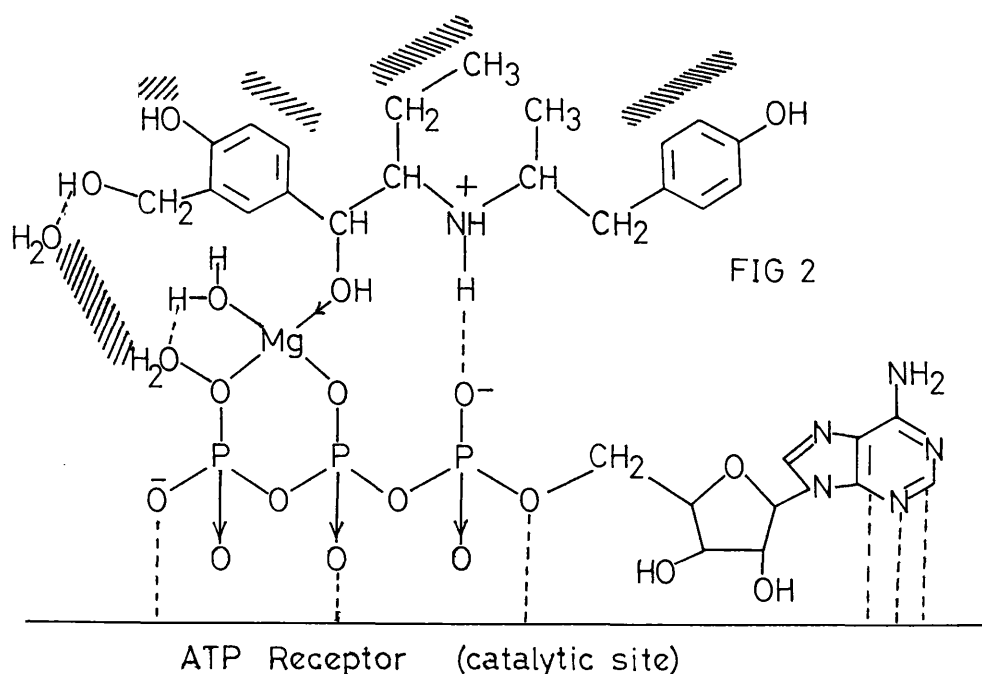
the fundamental features required to activate them). It has also been found that cyclic AMP produces pharmacological effects similar to those of β -receptor agonists, but which are not antagonised by β -blockers. Thus it has been postulated that activation of adenylyl cyclase is the prime function of β -receptor agonists.

The first detailed molecular explanation of agonistic activity has stemmed from this. Belleau^{2,12a} considered that β -receptor agonists react directly at the active centre of the enzyme. He suggested that ATP was a part of the adrenergic receptor and proposed a mechanism that involves interaction of the catecholamine with magnesium and ATP to catalyse the conversion into cyclic AMP, by adenylyl cyclase. The formation of cyclic AMP would involve attack by the 3-hydroxy group of the ribose moiety on the innermost phosphorus atom of ATP with expulsion of the pyrophosphate residue (FIG I).

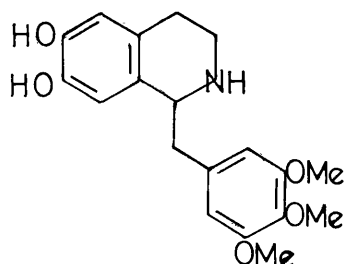
FIG I



It is suggested that β -receptor agonists catalyse this reaction because their cationic head neutralises the negative charge on the inner phosphate anion, thus increasing the electrophilic character of the phosphorus atom i.e. the rate of nucleophilic displacement of the 3-hydroxy group of the ribose moiety, is enhanced. The absolute requirement for β -receptor agonism is then, a cation correctly aligned with the appropriate phosphate group in ATP and the role of the other functional groups in β -receptor agonists is to increase the likelihood of this event. The catechol function facilitates this alignment by chelation with the divalent magnesium ion bound to phosphate groups in ATP, and the non-polar N-substituent, by bonding with the adenine moiety. Certain refinements to this model have been advanced by Belleau and are summarised in Fig. 2. This representation seeks to describe the observed structure-activity relationships for most of the β -receptor agonists mentioned².



It was realised by Brittain et al² that trimetoquinol (7) cannot be fitted directly into this pattern since it lacks a



(7)

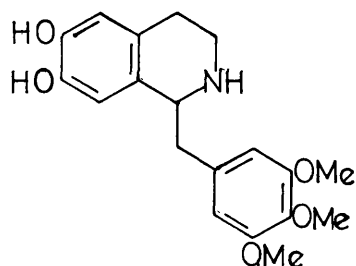
substituent corresponding to the β -hydroxy group. However, as the indispensable feature for β -receptor agonist activity is a strong secondary base, and if the function of the remainder of the molecule is to effect optimal orientation of the receptor complex then, they suggest², the more rigidly held basic group of the isoquinoline no longer requires other points of attachment.

Iwasawa and Kujimoto^{9a} suggested that the trimethoxybenzyl group binds to the β -receptor in such a way as to fulfil the role of the β -hydroxy group. They went on to show that, as in isoprenaline, only the ~~laserotary~~ ^{levorotary} enantiomer is biologically active.

It was suggested² that such hypotheses as those of Belleau, as well as rationalising structure-activity relationships, can be used as a basis for the design of new, and possibly more effective β -receptor agonists.

2. Conclusion and aim.

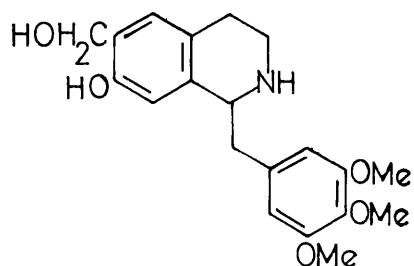
In the work described in this chapter, attention is focused upon the adrenergic β -receptor agonist trimetoquinol (7) which has a bronchodilator action five times more potent than



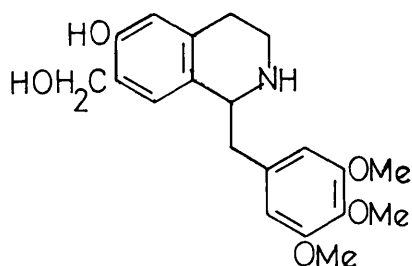
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isoprenaline (3) in vivo, and a less marked effect on the cardiovascular system. The activity of trimetoquinol has been demonstrated in man, but has a very short duration of action, probably due to it being a substrate for catechol-o-methyl transferase (COMT),^{5a} so it is rapidly metabolised to an inactive molecule. Replacement of one of the phenolic groups of isoprenaline (3) by a hydroxymethyl group and a change of N-Pr to N-Bu gives salbutamol (6) which has an

improved profile of activity and which is stable to COMT^{5a,b}. It was decided therefore to prepare the corresponding hydroxymethyl derivative (14). On the basis of the structure-activity relationships so far discussed it can be predicted



(14)



(15)

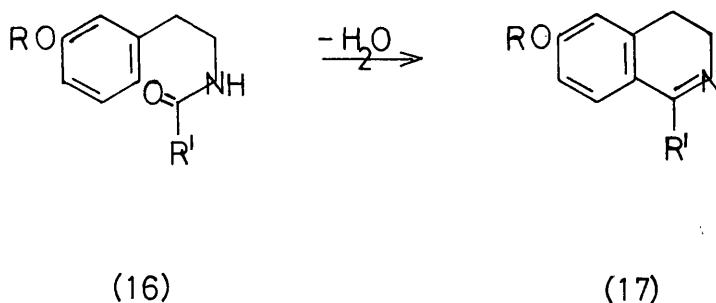
that only one of the derivatives (14) and (15) would possess the desired activity, and that this compound should be (14) having a para-hydroxyphenylethylamine part structure. At the outset of this work the isomer (15) had been synthesised¹³ and shown to possess little activity so the subject of Chapter 1 of this thesis therefore is the synthesis of 6-hydroxymethyl-7-hydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (14).

3. Synthetic methods available for isoquinoline synthesis.

The majority of the standard procedures for synthesising the isoquinoline ring system depend on acid-catalysed cyclisation of an aromatic ring onto a carbonium ion^{14a,b,c}. These reactions are facilitated by electron donating groups in the aromatic nucleus ortho and para to the point of cyclisation.

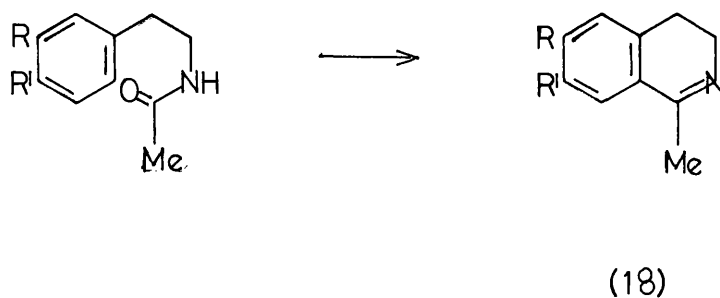
Bischler-Napieralski Reaction^{14a,15}

This is one of the most popular methods and involves the cyclodehydration of β -phenethylamides of the type (16) to 3,4-dihydroisoquinolines (17). Reagents such as phosphorus pentoxide, phosphorus pentachloride, phosphorus oxychloride



or anhydrous zinc chloride are commonly employed in this reaction. When the position para to the electron releasing group is available, ring closure invariably occurs at that position. However, if this site is blocked the ortho position may be attacked¹⁶.

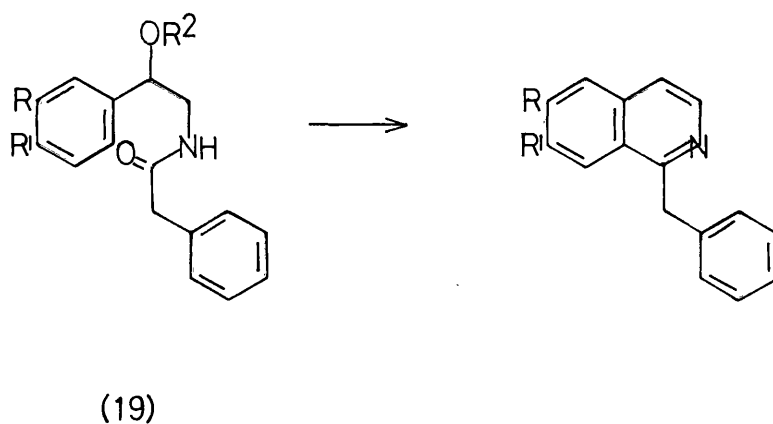
It has been found^{14a} that the yield of (18) when $R=R'=H$, is only a small fraction of that obtained when $RR'=\text{OCH}_2\text{O}$. It has been demonstrated that the presence of an electron



attracting group in the aromatic ring does not prevent the reaction, altogether.

Pictet-Gams Reaction^{14a}

This is an important variation of the Bischler-Napieralski reaction and involves formation of the aromatic isoquinoline directly from a β -hydroxy or β -methoxy- β -phenylethylamide (19) by treatment with acidic reagents. This conversion involves

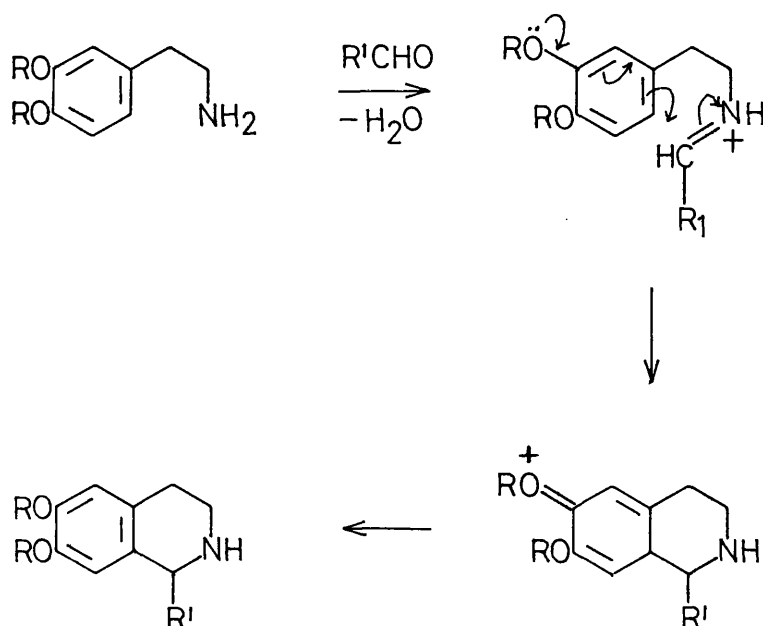


dehydration or removal of methanol prior to cyclisation as in the Bischler-Napieralski reaction.

Pictet-Spengler Reaction¹⁴.

This method, in its simplest form, involves the condensation of a β -arylethylamine with a carbonyl compound under acid conditions, to give a 1-substituted 1,2,3,4-tetrahydroisoquinoline. The mechanism (Scheme I) implies the same dependence on electron

Scheme I



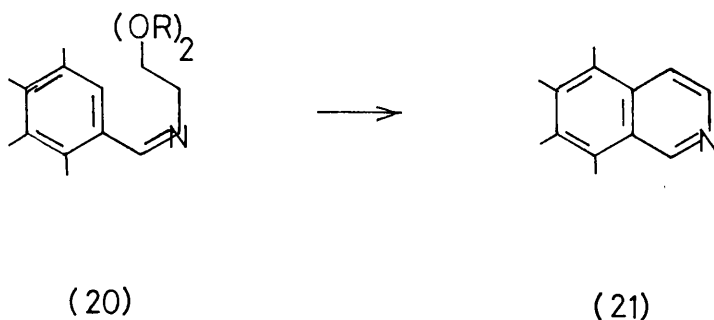
density at the position of ring closure as is found in the two previous reactions. Experimental results support this, in that the absence of such activation results in either little or no yield of the required product.

Although acidic conditions are normally employed in the Pictet-Spengler reaction, phosphorus pentoxide in pyridine has been successfully used by Kametani¹⁸. He also found that no catalyst at all was required in one system which possessed a

phenolic group para to the position of ring closure. This supports an earlier demonstration that ring closure on such activated systems will occur under physiological conditions¹⁹.

Pomeranz-Fritsch Reaction^{14c}

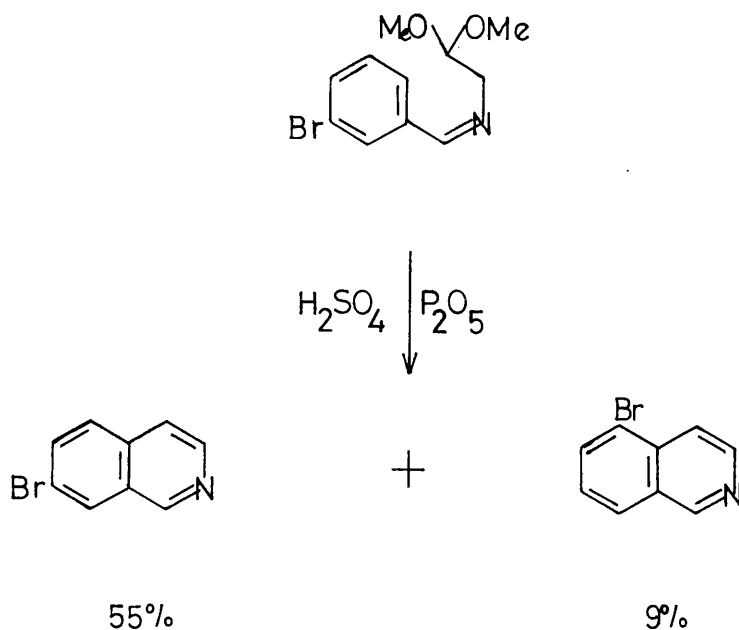
This involves the acid-catalysed cyclisation of benzal-aminoacetals (20) and results in the formation of the aromatic isoquinoline nucleus (21). The most common reagents used are



concentrated sulphuric acid, or sulphuric acid mixed with other acid reagents. Yields of cyclised product are variable, being generally low, especially in deactivated systems and highly dependent upon acid concentration. Meta-alkoxy and meta-hydroxy derivatives, which possess a para position accessible to the attacking carbonium ion, react under relatively mild conditions²⁰ whereas compounds with a nucleus of low activity such as nitrobenzalaminocetaldehydedialkylacetals fail to react at all^{14c}.

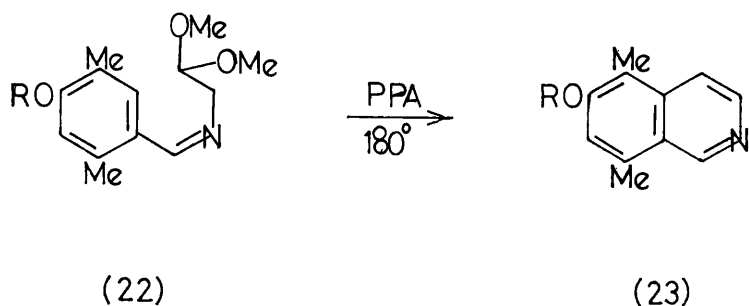
The Pomeranz-Fritsch reaction differs from the methods so far discussed in that ring closure ortho to the aromatic

activating group has been reported to take place in addition to the expected para ring closure. As in the example cited below²¹, the para ring closure predominates. Subsequent work



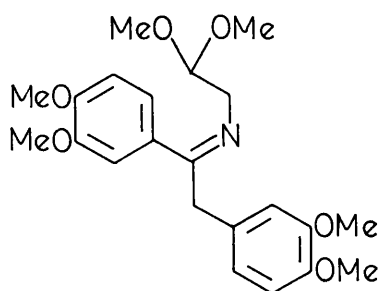
by Mathison²² however, fails to corroborate this finding.

Of the other acidic reagents^{23a,b} used in the Pomeranz-Fritsch reaction, polyphosphoric acid²⁴ has probably enjoyed the most success, although in the main, yields have been less than 50%^{23b}. In an exceptional example²⁵ a 98% yield of (23, $\text{R}=\text{CH}_3$) was obtained, but the unpredictable nature of the reaction was

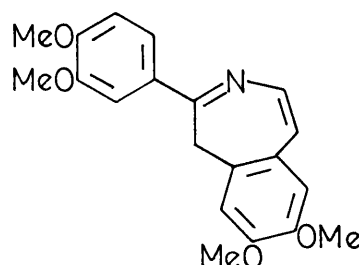


illustrated when none of the phenolic isoquinoline (23, R=H) was isolated from the reaction of (22, R=H) under the same conditions of cyclisation.

An attempted modification of this reaction involved the cyclisation of a benzylbenzalaminoacetal of the type (24), but this afforded the benzazapine (25)²⁶. The main side reaction



(24)

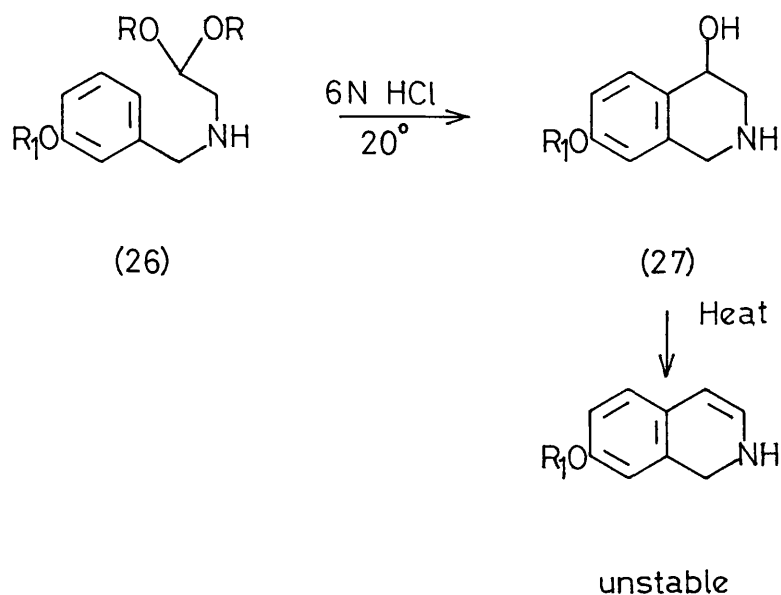


(25)

in the Pomeranz-Fritsch reaction, however, is the acid-catalysed hydrolysis of the Schiff's base to the starting aldehyde and amine.

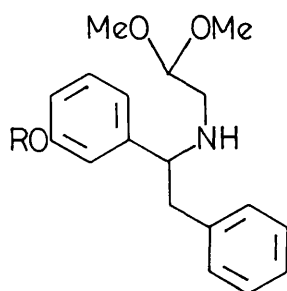
Bobbitt Reaction²⁷.

A valuable modification of the Pomeranz-Fritsch reaction by Bobbitt et al overcame this problem by carrying out the cyclisation procedure on the reduced aminoacetals such as (26)²⁸. Although at lower temperatures the 4-hydroxy-1,2,3,4-tetrahydro-isoquinoline (27) can be isolated,²⁹ Bobbitt showed that catalytic hydrogenation of the acid solution of the acetal gives

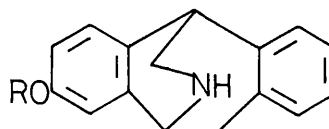


1,2,3,4-tetrahydroisoquinolines³⁰. An oxygen function in the meta position of the aromatic ring of the acetal (26) is necessary for cyclisation, and yields based on vanillin, isovanillin and orthovanillin are 71%, 67% and 75% respectively. The fully aromatic isoquinolines may be formed by catalytic dehydrogenation of the tetrahydroisoquinolines or, preferably by treatment of the 4-hydroxy-1,2,3,4,-tetrahydroisoquinoline (27) consecutively with N-bromosuccinimide and mineral acid³¹.

A limitation of the Bobbitt modification involves the acid-catalysed cyclisation of benzylbenzylaminoacetal of the type (28). However, there is a high probability that double cyclisation to the isopavine ring system (29) might take place³².

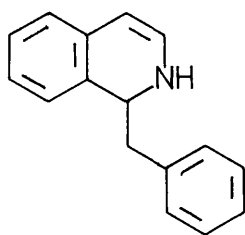


(28)

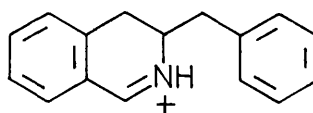


(29)

Such behaviour has been exploited in these laboratories in the preparation of naturally occurring isopavines^{33a,b} and is the subject of the work described in Chapter 2 of this thesis. An intermediate in this double cyclisation is the 1,2-dihydroisoquinoline (30) which, under acid conditions can rearrange to the 3-benzyl-3,4-dihydroisoquinolinium salt (31)³⁴. This reaction is discussed in detail in Chapter 3 of this treatise.

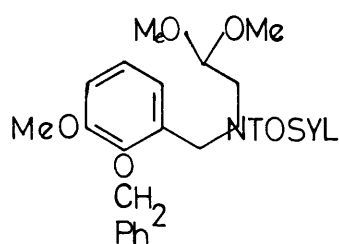


(30)

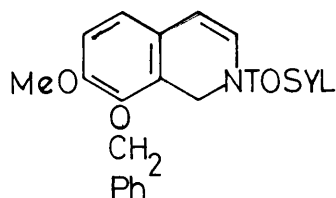


(31)

A further modification of the Pomeranz-Fritsch reaction has been described by Jackson and Stewart³⁵, whereby cyclisation of the N-tosyl acetal (32) with acid has afforded the stable N-tosyl-1,2-dihydroisoquinoline (33) which on treatment with base gives the aromatic isoquinoline (34) in good yield. At the time of this work the scope of this reaction had not been



(32)



(33)



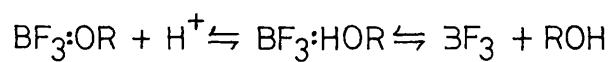
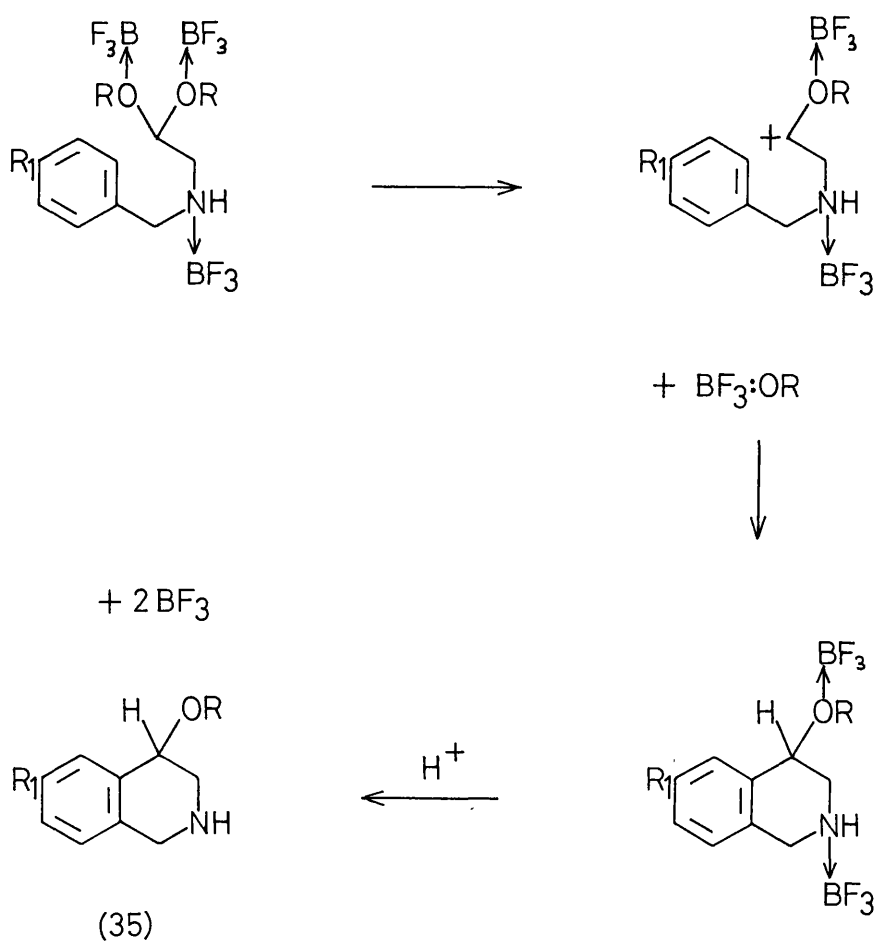
(34)

investigated but the sulphonyl grouping appears to stabilise the 1,2-dihydroisoquinoline significantly.

A further cyclisation of acetals of the type (26) has been achieved by Vinot and Quelet^{36a,b} who demonstrated that with

boron trifluoride the reaction proceeds to a 4-alkoxy-1,2,3,4-tetrahydroisoquinoline (35), subsequent treatment of which with palladium on carbon gives the aromatic isoquinoline. The proposed mechanism of cyclisation, Scheme 2, suggests less need for ring activation than in the previous examples cited. Unfortunately the reaction does not proceed well when the

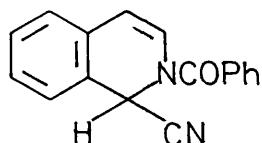
Scheme 2



benzene ring is oxygenated, owing to the formation of a complex with boron trifluoride. In addition, poor results have been obtained when the electron releasing substituent in the aromatic ring is not meta to the point of ring closure.

Reissert Reaction^{38a,b}

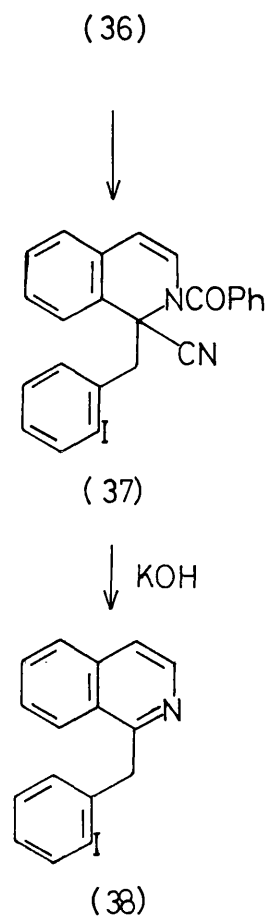
Of the methods so far discussed some can provide a 1-benzyl isoquinoline derivative directly, but others, notably the Pomeranz-Fritsch reaction and its modifications cannot. The most suitable method for the introduction of a substituent at C₁ of a preformed isoquinoline nucleus might be the Reissert reaction. This involves the formation of an N-acyl-1,2-dihydroisoquinolal donitrile or "Reissert compound" of the type (36) by reaction of an aromatic isoquinoline with potassium cyanide and benzoyl chloride in dichloromethane and water.



(36)

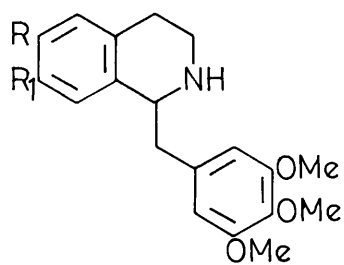
Removal of the hydrogen at C₁ as a proton with sodium hydride in dimethylformamide³⁹, aqueous sodium hydroxide⁴⁰, or phenyllithium⁴¹, gives an anion which will react with a wide range of compounds bearing an active halogen atom. For example reaction with a benzyl halide gives an "alkylated

Reissert compound" such as (37) which on treatment with base yields the 1-benzyl isoquinoline (38)^{39b}.



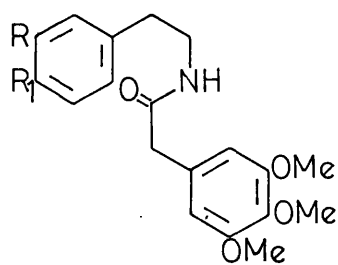
4. Conclusions

With these methods available it is in order to review the objective, namely the synthesis of (14).



(14) $R = \text{CH}_2\text{OH}$, $R_1 = \text{HO}$

(15) $R = \text{OH}$, $R_1 = \text{CH}_2\text{OH}$



$R = \text{COOMe}$, $R_1 = \text{OH}$ (40)

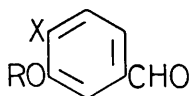
$R = \text{OH}$, $R_1 = \text{COOMe}$ (39)

Whereas isomer (15) was prepared¹³ by the Bischler-Napieralski type of cyclisation of the amide (39), the appropriate precursor (40) to the required isomer (14) does not contain the requisite electron donating substituent para to the position of ring closure. For this same reason the Pictet-Spengler and Pictet-Gams modifications are unsuitable.

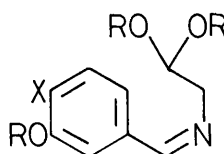
In view of the problems inherent with cyclisation of benzylbenzylaminoacetals and benzylbenzalaminoacetals it was decided that the aromatic isoquinoline ring system, unsubstituted at C₁ should be prepared and elaborated via the Reissert reaction.

It was considered that the most straight forward synthesis of (14) would require as starting material, an aldehyde of the type (41) in which the grouping X is stable to all of the synthetic steps of the proposed sequence and yet readily converted, at an appropriate stage, into a hydroxymethyl function. The commercially available metacresotinic acid (42) appeared to be a suitable precursor and Scheme 3 summarises the reaction sequence envisaged at the outset of this work.

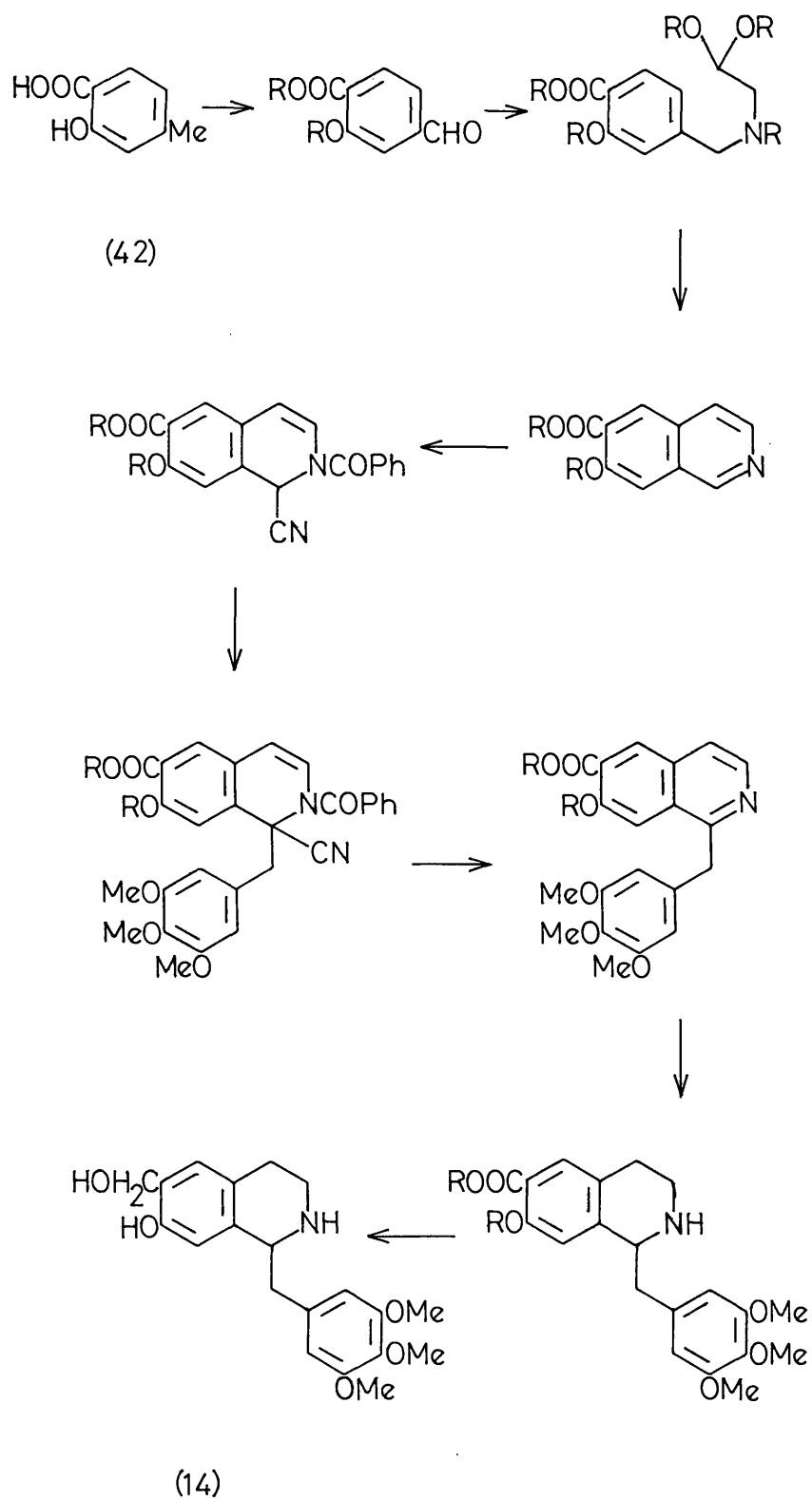
In view of the unpredictable nature of the Pomeranz-Fritsch reaction it was decided, at this stage, not to attempt to cyclise a benzalaminoacetal of the type (43). Furthermore,



(41)



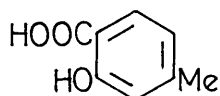
(43)



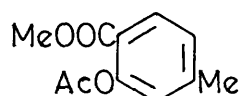
the Vinot-Quelet method was rejected in favour of the Bobbitt modification which had been employed successfully in these laboratories. It was hoped that the N-tosyl method due to Jackson could be used to extend the scope of this modification.

DISCUSSION1. Synthesis of saligenin (14)

Metacresotinic acid (42) was converted in good yield to its ester acetate (44) by standard procedures. Oxidation of the tolyl function was effected by a laborious method due to

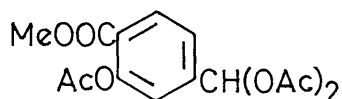


(42)

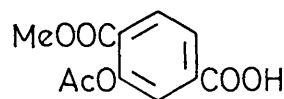


(44)

Thiele⁴² which involves treatment of (44) with a solution of chromium trioxide in glacial acetic acid, acetic anhydride and concentrated sulphuric acid to afford the aldehyde triacetate (45). This shows a hydrogen singlet in its NMR spectrum at 7.68 δ assigned to the methine proton. Optimum yields were obtained by maintaining the reaction temperature between -10° and -15° , whereby less than 5% of the acid (46) was isolated compared with 54% of (45).

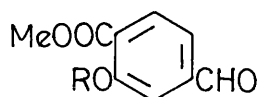


(45)

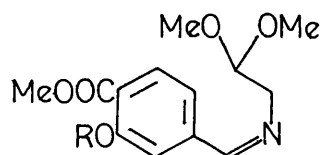


(46)

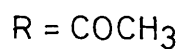
The Hydrolysis of (45) to the aldehyde monoacetate (47) was accomplished, in 75% yield, with a mixture of acetic acid and hydrochloric acid. Subsequent condensation of (47) with aminoacetaldehydedimethylacetal gave only 70% conversion to the Schiff's' base (48), under conditions of heating under reflux in benzene. In an alternative approach hydrolysis of



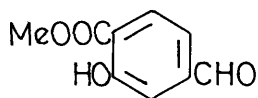
(47)



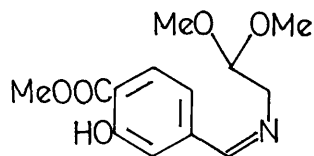
(48)



the triacetate (45) with methanolic sulphuric acid afforded a good yield of the phenolic aldehyde (49) which was converted smoothly, in 90% yield, to the Schiff's' base (50). This



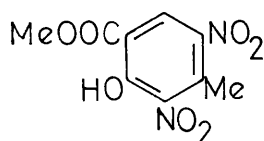
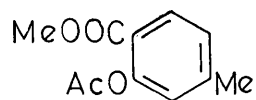
(49)



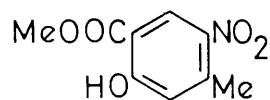
(50)

compound crystallised from petroleum ether and showed a characteristic C=N absorption at 1650cm^{-1} in its infrared (I.R.) spectrum, and a hydrogen bonded ester function absorbing at 1680cm^{-1} .

Parallel to this work a more efficient method was investigated for oxidation of the tolyl function of (44). Following the work of Trehanovsky and Young⁴³, who used ceric ammonium nitrate (C.A.N) in 50% aqueous acetic acid to convert *p*-xylene into *p*-tolylaldehyde in 73% yield, compound (44) was subjected to the same conditions. The product was shown by thin layer chromatography (T.L.C.) to be a mixture of two components, neither of which exhibited an aldehydic carbonyl absorption in the I.R. spectrum. Separation of the mixture by preparative layer chromatography (P.L.C.) afforded two crystalline solids, the I.R. spectra of each exhibiting strong bands in the 1550 and 1350cm^{-1} regions. The N.M.R. spectra of both compounds showed the presence of the tolyl function, the methyl ester group and a phenolic hydroxy group. In addition to this, one contained one aromatic proton (8.63δ) and the other contained two (8.64δ , 6.92δ). On the basis of this evidence structures (51) and (52) were assigned to the two products which were shown by mass spectrometry (M.S.) to possess molecular weights of 256 and 211 respectively.



(51)

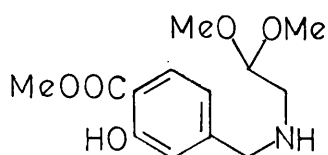


(52)

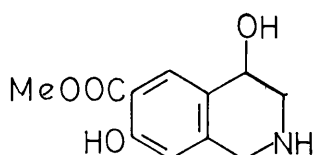
Nitric acid liberated in the reaction presumably effects the observed nitration, but no parallel reaction could be traced in the literature, although ceric ion oxidations are well reviewed⁴⁴. Since no oxidation to the required aldehyde was observed this investigation was abandoned in favour of the Thiele method.

It was found that the Schiffs' base (50) could be converted either by catalytic or chemical reduction using sodium borohydride into the benzylaminoacetal (53). However, this compound resisted cyclisation under a variety of conditions. The 4-hydroxy

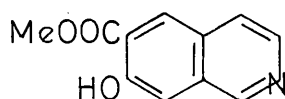
derivative (54) could not be detected, and treatment of the gummy reaction products with N-bromosuccinimide, followed by mineral acid afforded no trace of the aromatic isoquinoline (55).



(53)

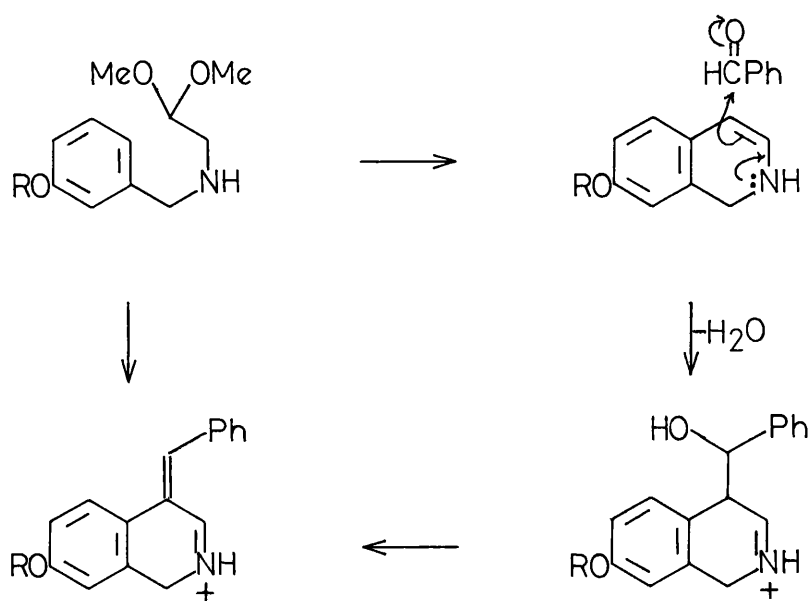


(54)



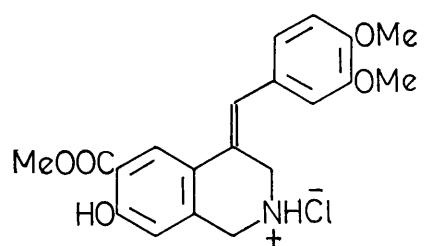
(55)

A technique, first reported by Bobbitt et al²⁹ and adapted in these laboratories for the synthesis of 4-benzyl-isoquinoline compounds⁴⁵, involves the acid-catalysed cyclisation of an acetal in the presence of an aromatic aldehyde. The reaction takes place via an unstable 1,2-dihydroisoquinoline intermediate⁴⁶ as shown in Scheme 4. In order to establish whether cyclisation of the acetal (53) was taking place, acid treatment was carried out in the presence of veratraldehyde;



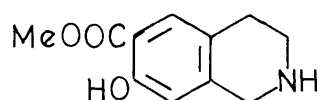
Scheme 4

but only a small quantity of the exocyclic salt (56) was



(56)

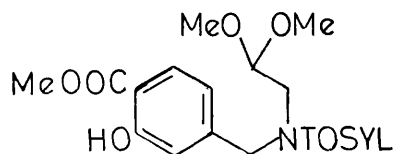
isolated and this from reaction with seven normal methanolic hydrochloric acid heated under reflux for two hours. This was taken as an indication that cyclisation would require acidic conditions too vigorous for the stability of a 1,2-dihydroisoquinoline intermediate. Even hydrogenolysis of an acid solution of the acetal gave none of the required tetrahydroisoquinoline (57) when carried out at a range of temperatures up to 90°.



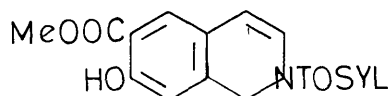
(57)

N-sulphonyl Route.

It was considered that cyclisation of the N-tosylacetal (58) might afford a 1,2-dihydroisoquinoline derivative that is stable to the acid conditions required for its formation. Reaction of the acetal (53) with p-toluenesulphonyl chloride in pyridine gave (58), which showed strong absorptions in its I.R. spectrum



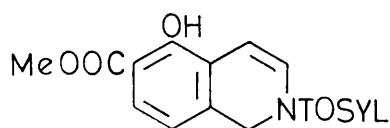
(58)



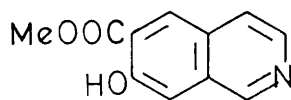
(59)

at 1345 and 1168cm^{-1} expected for the tosyl group. When (58) was subjected to prolonged acid treatment the desired ring closed compound (59) was obtained, which showed in its N.M.R. spectrum two aromatic singlet absorptions and an AB pattern in the olefinic region. A high resolution mass measurement of the molecular ion confirmed the molecular formula to be $\text{C}_{18}\text{H}_{17}\text{NO}_5\text{S}$. Yields of the cyclised material were variable but generally between 50% and 70%.

An investigation of the mother liquors afforded no evidence for any ring closure ortho to the phenolic grouping to give (60).



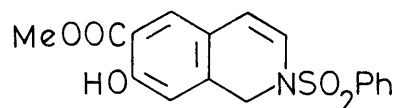
(60)



(61)

Once formed, however, the N-tosyl compound (59) resisted all attempts to convert it into the aromatic isoquinoline (61). The reported technique,³⁵ which involves potassium t-butoxide in t-butanol returned unchanged starting material as indeed did most of the methods used (see experimental section page 76).

It was hoped that a modification of the sulphonyl moiety might facilitate aromatisation. However, the methanesulphonyl analogue of (58) could not be formed, and although cyclisation of the benzene sulphonyl compound afforded the required 1,2-dihydro derivative (62), this proved to be as stable to base as the N-tosyl analogue (59). Some difficulties were

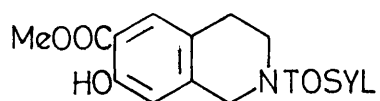


(62)

encountered due to the insolubility of the phenate salts of (59) and (62), but all attempts to protect the phenolic function were unsuccessful.

It was reasoned that acid hydrolysis could be employed to remove the sulphonyl grouping, but that this would of necessity produce an unstable 1,2-dihydroisoquinoline. In an attempt to eliminate this possibility hydrogenation of (59) in acetic acid at 60° over palladium on carbon was tried, but this only afforded a poor yield of the reduced derivative (63) which could not be obtained analytically pure. Reaction of (63),

however, with acid gave no isolable products, so the otherwise

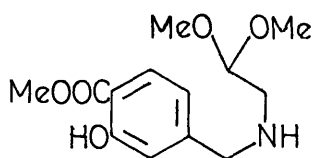


(63)

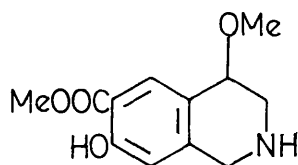
attractive sulphonyl route was abandoned.

Attempted cyclisation with Boron Trifluoride.

Parallel to this work some attempts at the Vinot type of cyclisation were carried out, but the acetal (53) in dichloromethane and boron trifluoride afforded at best a gum,



(53)

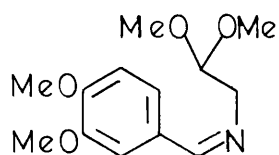


(64)

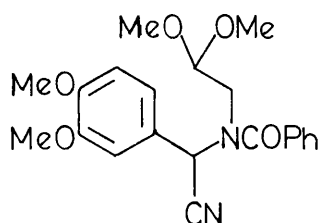
the mass spectrum (M.S.) of which indicated the presence of the 4-methoxy-1,2,3,4-tetrahydroisoquinoline (64). This material resisted attempts at purification so no further effort was

concentrated on this route.

At this stage a piece of speculative chemistry was undertaken following demonstration in these laboratories^{33a} that the Schiff's base (65) would form a Reissert compound (66). The action of mineral acid on Reissert compounds is known to

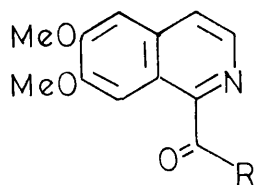


(65)



(66)

produce benzaldehyde and isoquinaldic acid derivatives⁴⁷, so it was considered that acid treatment of (66) might, by cyclisation and hydrolysis, afford a compound of the type (67). However, the results were disappointing and although there was some

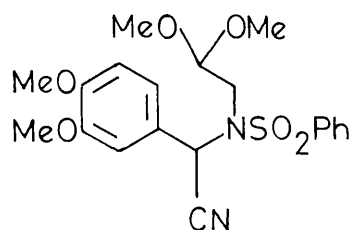


(67)

- (a) R=OH
- (b) R=NH₂
- (c) R=OMe

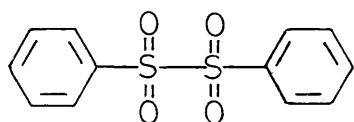
spectroscopic evidence for the formation of (67b) and (67c) separation and purification proved impossible.

It was further reasoned that a model "sulphonyl Reissert compound"⁴⁸ (68) might be formed by the reaction of the Schiff's base (65) with potassium cyanide and benzenesulphonyl chloride.

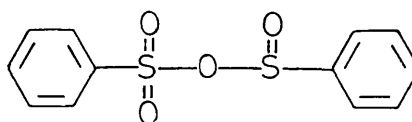


(68)

From this it was hoped to obtain an isoquinaldic acid derivative such as (67). However, (68) could not be prepared and the only product isolated from the reaction was a white crystalline solid m.p. 189-9° which analysed for $C_{12}H_{10}S_2O_4$. Of the two possible isomeric structures, the disulphone (69) melting point



(69)



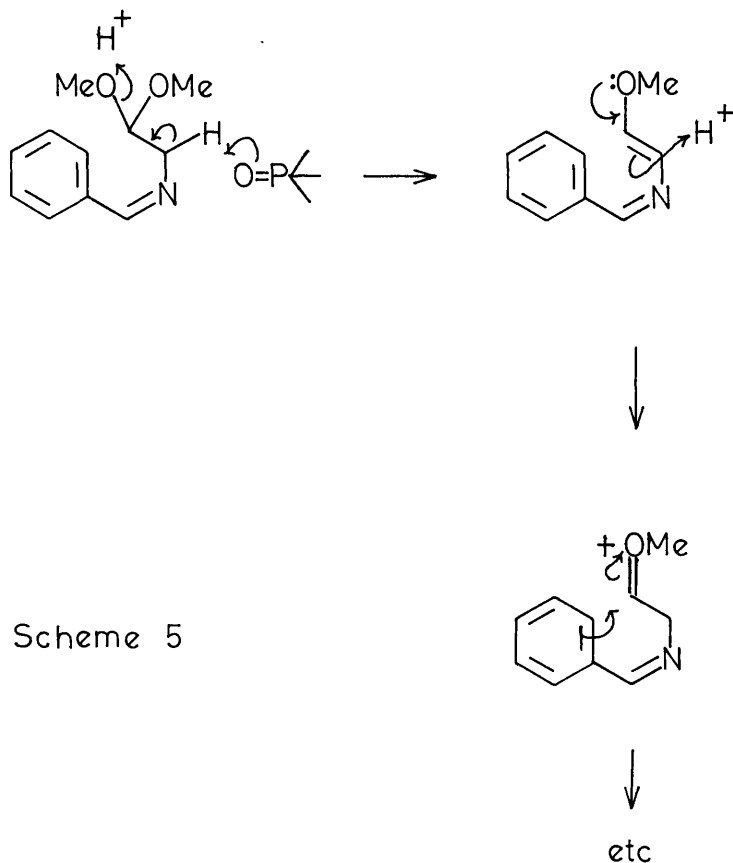
(70)

196°⁴⁹ and 193°⁵⁰ and the anhydride (70) melting point 93-5°⁵¹, the former seems the more likely. Further evidence for this structure is provided by the I.R. and N.M.R. spectral data which

of two components, which were subsequently separated by P.L.C. into two crystalline solids and assigned the structures (61) and (71). Compound (71) is the product from ring closure ortho to the phenolic group. The N.M.R. spectrum of each of the isoquinolines possessed a peak at 9.1δ attributable to C_1-H , and an AB splitting pattern for the C_3H , C_4H system. In addition to the ester methyl absorption at 4.0δ and the deuterable phenolic group, compound (61) possessed two aromatic singlet absorptions at 8.34δ and 7.34δ , whereas (71) showed an AB pattern centred at 7.77δ and 7.28δ attributable to C_7H and C_8H . The required isomer (61) was predominant over (71) by a 5:3 ratio. U.V. spectra of various standard mixtures of the two isoquinolines gave a rapid means of monitoring the isomer ratio and this was used to examine the products from a range of sulphuric acid catalysed cyclisations (see experimental section, page 79). The main problem, even at high acid concentrations, seemed to be caused by hydrolysis of the Schiff's base to the aldehyde, and in order to overcome this, polyphosphoric acid was used as the cyclisation reagent, with much more success. When the reaction temperature was maintained between 70° and 100° , 24% of (61) and 70% of (71) were achieved. Although reaction at lower temperature afforded proportionally more of the desired isomer (61), the overall yield of bases was low.

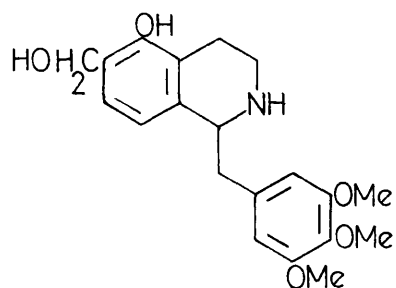
Other reagents were used in a search for a more favourable product ratio as well as good conversion and are summarised in the experimental section, page 79 .

It has been proposed^{23b} that polyphosphoric acid facilitates cyclisation as shown in Scheme 5, although in most examples



cited yields have been considerably less than the conversion obtained in this example. The proportion of ortho ring closure observed is also anomalous.

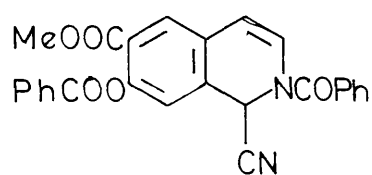
Appropriate seeding of a solution containing a mixture of isoquinolines afforded (61) and (71) in a pure state and in this way the planned synthesis was continued with a view to the preparation of the additional saligenin (72).



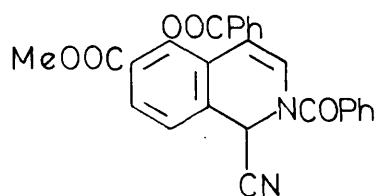
(72)

Reissert reaction.

The isoquinolines (61) and (71) were converted into their corresponding N-benzoyl-1,2-dihydroisoquinaldonitriles (73) and (74) by treatment with potassium cyanide and benzoyl chloride in dichloromethane and water. It is somewhat surprising that the o-benzoates were formed in view of the earlier unsuccessful



(73)



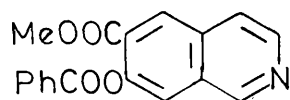
(74)

attempts to protect the phenolic function (see page 83).

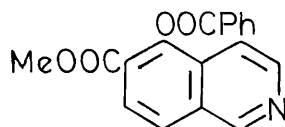
The Reissert compounds (73) and (74) formed in less than 10% yields under normal reaction times, and the best yields that

could be obtained were 20-25% after twenty four hours reaction. Each of these compounds, in its N.M.R. spectrum exhibits a one proton singlet absorption (7.1δ) attributable to the C_1 -H. The aromatic absorptions, in both spectra, correspond to twelve protons separate from the AB pattern observed for the olefinic protons. In the spectrum of (74) the aromatic pattern is discernable whereas two, one proton singlets are evident in the spectrum of isomer (73).

The main products from these reactions however were non-phenolic bases which possessed u.v. spectra typical of the aromatic isoquinoline structure. Carbonyl absorptions were present in the I.R. spectra at 1740 and 1730cm^{-1} and both compounds were shown to have the constitution $C_{18}H_{13}NO_4$. On the basis of this evidence the benzoate structures (75) and (76) were assigned. Treatment of (75) with 30% sodium hydroxide

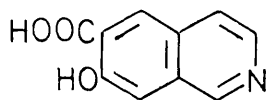


(75)



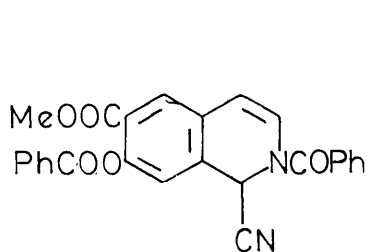
(76)

gave 7-hydroxy-6-isoquinoline carboxylic acid (77).

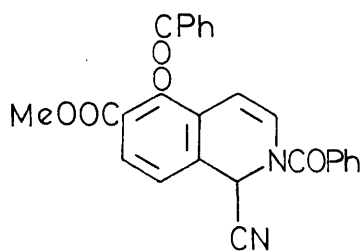


(77)

Available literature suggests that the use of the water-dichloromethane system^{23a,b} is the preferred method for Reissert compound formation, and although some have been reported to form in water, this technique afforded (73) and (74) in yields of 10-15%. Furthermore, attempts to protect the



(73)

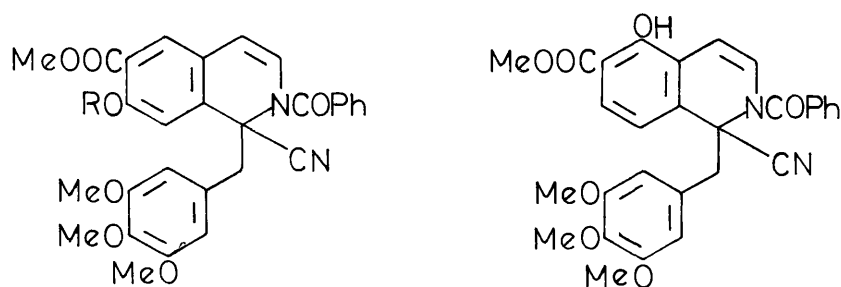


(74)

phenolic group of the isoquinolines, as benzyl ethers, with a view to improving the conversion, all resulted in failure (see experimental section page 83).

Alkylation of the Reissert compounds (73) and (74).

Alkylation of (73) with 3,4,5-trimethoxybenzyl chloride was effected with sodium hydride and dimethylformamide. The product, however, appeared by I.R. and M.S. to be a mixture of the phenolic compound (75a) and the benzoate (75b). Addition of an extra equivalent of base to the reaction and prolonged



(75)a R=H

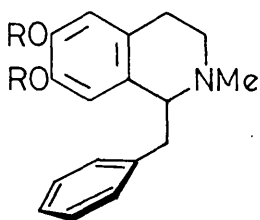
b R=COPh

c R=CH₂C₆H₂(OMe)₃

(76)

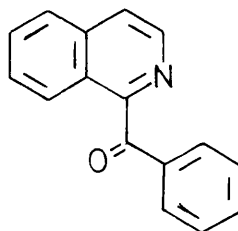
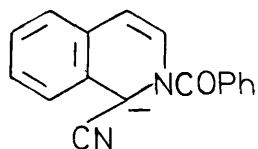
reaction time enabled the phenolic compound to be isolated in good yield. A trace amount of the 3,4,5-trimethoxybenzyl ether (75c) was detected by M.S., but was easily removed on recrystallisation. In an exactly analogous manner isomer (76) was obtained in high yield. Each of the I.R. spectra of (75a) and (76) shows two carbonyl absorptions, that due to the amide at 1640cm⁻¹ and that due to the intramolecularly hydrogen bonded ester at 1675cm⁻¹. Typically^{38a,b} the nitrile absorptions are too weak to be evident. The M.S. of the two compounds show low intensity molecular ions at 514 m/e, with a high intensity peak at 373 m/e corresponding to the loss of the benzoyl group (105 m/e) and the nitrile group (26 m/e). The N.M.R. spectra,

reproduced on page 68 , are consistent with the proposed structures, but show C_8-H to absorb at 6.83δ in (75a) and either 7.70 or 6.92δ in (76). One might, however, have expected ring C to have shielded this position to a position nearer 6δ (see page 149 of this thesis). It must be concluded therefore that ring C in this type of compound takes up a conformation different to that observed in l-benzylisoquinolines of the type (77).



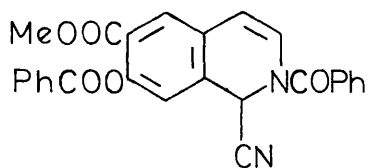
(77)

It is known^{38b} that N-acylisoquinaldonitriles in sodium hydride and dimethylformamide can undergo an N to C_1 migration of the benzoyl group to give a l-benzoyl isoquinoline of the type (78). It was suggested⁵² that systems in which the anion is destabilised are most prone to this behaviour. No migration products were detected in the alkylation reactions

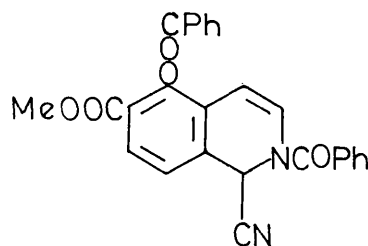


(78)

of (73) or (74), perhaps because of the carboxyl function at



(73)



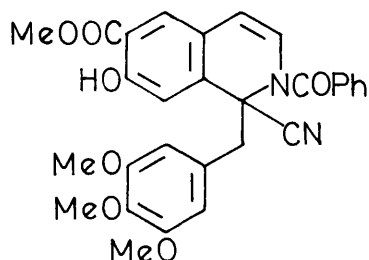
(74)

C_6 further stabilising the anion. The position of the C_1 -H absorption in the N.M.R. spectra of the two compounds (7.1 δ) supports an increased acidity compared with other Reissert compounds in which this absorption is rarely downfield of 6.6 δ ⁵³.

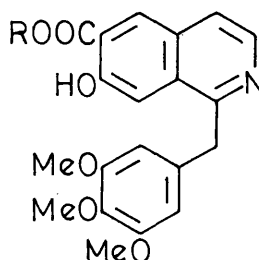
Generation of the aromatic isoquinoline nucleus.

Alkylated Reissert compounds are normally converted into aromatic isoquinoline derivatives with alcoholic sodium hydroxide at steam bath temperature⁵⁴. However, when this technique was applied to (75a) only complex mixtures were obtained.

It was noted that traces of the aromatic isoquinoline (78)



(75a)



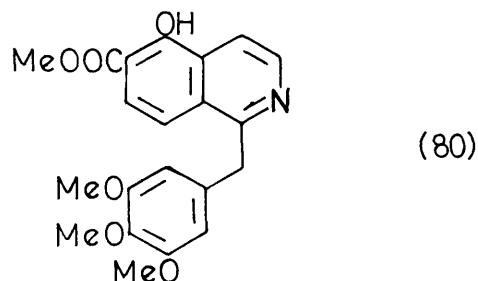
(78) R=Me

(79) R=H

were produced in the alkylation reaction of (73) and this prompted the use of sodium methoxide in methanol at room temperature to achieve the required conversion (75a) to (78). In model experiments, yields of up to 95% of 1-benzylisoquinoline were obtained from the reaction of N-benzoyl-1-benzylisoquinolaldehyde nitrile with this reagent. This represents an improvement in yields on methods reported to date⁵⁴. In this way (75a) was converted smoothly into the desired 1-benzylisoquinoline (78), although some saponification at C₆ was observed to give the acid (79). Although this resisted esterification to (78) in methanol

and sulphuric acid, the conversion was achieved in hot methanol with hydrogen chloride gas as catalyst.

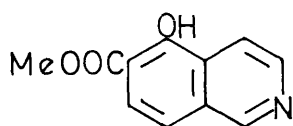
As a point of practical interest, isolation of the alkylated Reissert compound (75a) was unnecessary. Instead, alkylation, hydrolysis and re-esterification of the C₆ carboxyl group can be achieved in a "one-pot" reaction to afford the 1-benzyl-isoquinoline ester (78) in good yield. By an exactly analogous route, methyl 5-hydroxy-1-(3,4,5-trimethoxybenzyl)-isoquinoline-6-carboxylate (80) was prepared.



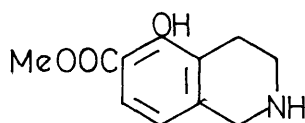
Both isomers (78) and (80) exhibit a u.v. spectrum typical of an aromatic isoquinoline (λ_{max} 383nm), and showed by I.R., the presence of a salicylic ester grouping (3180 and 1683cm⁻¹). Both compounds were shown, by M.S., to possess the molecular weight (383), in accord with the structures assigned. The N.M.R. spectrum of each compound exhibits the methyl ester absorption at 4.0 δ , the benzylic methylene group as a broad singlet at 4.49 δ , and the three aromatic methoxyl groups

together at 3.77δ . Both isomers showed a typical AB splitting pattern for the C_3H-C_4H system (see page 69b). In the spectrum of compound (80), C_7H and C_8H are present as a pair of doublets whereas in the spectrum of (78) two singlet absorptions exist.

As a model for the reduction to the 1,2,3,4-tetrahydro derivatives, methyl 5-hydroxyisoquinoline-6-carboxylate (71) was successfully converted into (81) over Adams catalyst in

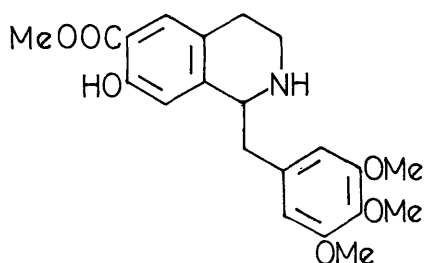


(71)

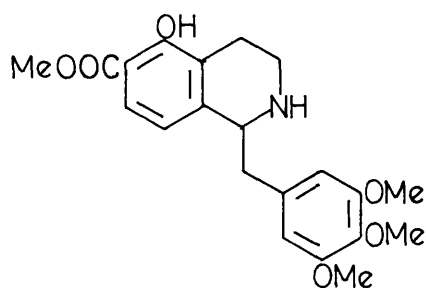


(81)

ethanol. The same treatment of (78) afforded a product which was shown by I.R. to have retained the ester function, and which exhibited no absorption maxima above 320nm. A complex six proton absorption between 3.6 and 2.6δ , and a broad triplet at 4.55δ corresponding to the hydrogen at C_1 support structure (82). In an



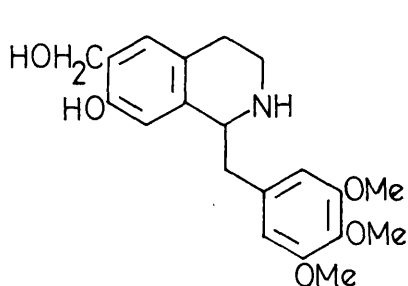
(82)



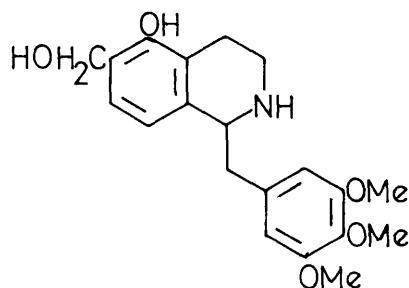
(83)

analogous manner (83) was obtained in good yield from isomer (80) and exhibited spectral characteristics in accord with the assigned structure.

Reduction of (82) with lithium aluminium hydride proceeded smoothly to give 51% yield of a crystalline product the I.R. spectrum of which showed no carbonyl absorption but strong absorption in the $3500\text{--}3200\text{cm}^{-1}$ region. The N.M.R. spectrum shows the aromatic protons at C_5 and C_8 to absorb as a broad singlet at 6.63δ compared with 7.62δ and 6.80δ in the precursor (82). There is no absorption due to the ester methyl group, this is replaced by a benzylic methylene group absorbing at 4.65δ . A broad three proton singlet at 5.5δ is removed on deuteration. On the basis of this, and mass spectral evidence for a molecular weight of 359, structure (14) was assigned to this compound.



(14)

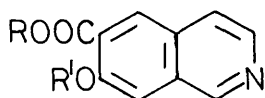


(84)

An analogous treatment of the isoquinoline (83) afforded, in 48% yield, the isomeric saligenin (84) the spectral data of which are consistent with this structure. In the N.M.R. spectrum C_7-H and C_8-H absorb as two very close doublets centred at 6.7δ .

2. Pharmacology of saligenins (14) and (84) and some isolated intermediates.

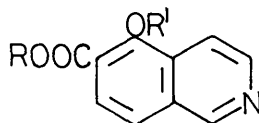
The saligenins (14) and (84) were screened by Allen & Hanbury Ltd., but were shown to possess no significant action as bronchodilators. In addition, their immediate precursors (82) and (83) were screened, with the isoquinolines listed below. None of these compounds showed any useful activity, and it seems



(61) $R=Me, R'=H$

(75) $R=Me, R'=COPh$

(77) $R=R'=H$



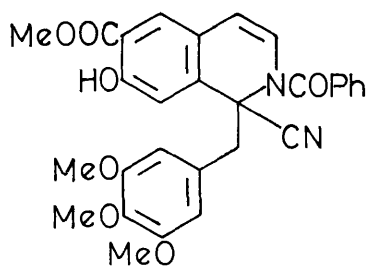
(71) $R=Me, R'=H$

(76) $R=Me, R'=COPh$

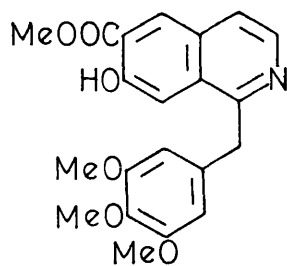
difficult to conclude anything about the theories of action of compounds in this field.

3. The isolation of an unexpected product.

On one occasion, an insitu treatment of the alkylated Reissert compound (75a) with sodium methoxide in methanol followed by methanol and hydrogen chloride afforded the

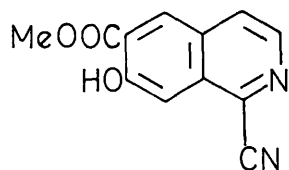


(75a)



(78)

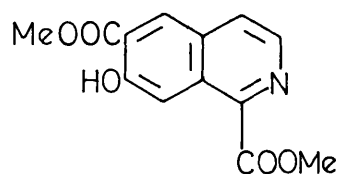
expected 1-benzylisoquinoline (78), contaminated with other components. P.L.C. afforded small amounts of two bases the u.v. spectrum of the first being typical of an aromatic isoquinoline. The I.R. spectrum showed absorptions at 3200, 1698 and 2200cm^{-1} , on the basis of which the cyano structure (85) was tentatively assigned. A high resolution mass



(85)

measurement of the molecular ion (228 m/e) confirms the required constitution of $C_{12}H_8N_2O_3$. The N.M.R. spectrum of this product is also in accord with the assigned structure.

The second base to be isolated exhibited a similar u.v. spectrum, but showed no nitrile absorption in the I.R. but an additional absorption at 1743cm^{-1} . The M.S. confirmed a molecular weight of 261, and the N.M.R. spectrum showed two methyl ester absorptions. On this basis, structure (86) was assigned to this second basic by-product. Since this work a 1-cyanoisoquinoline

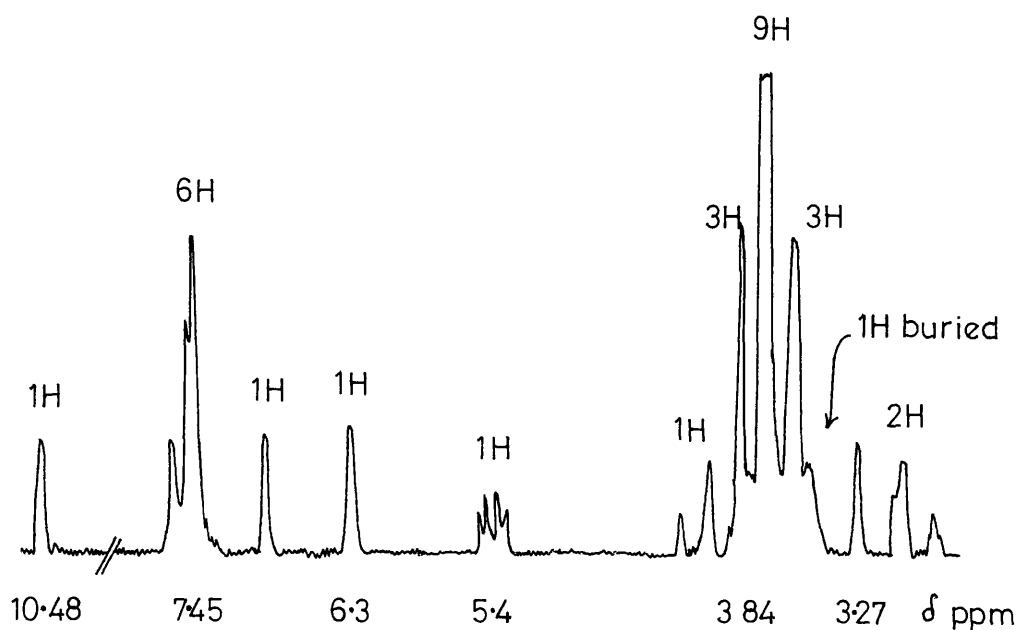


(86)

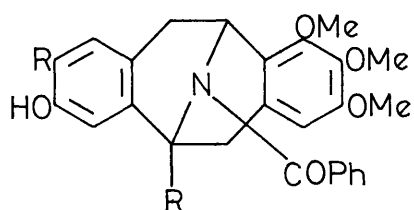
has been found⁵⁵ as a side product in the synthesis of a 1-benzyl-isoquinoline derivative via the Reissert method.

A third by-product (X), which was isolated by further chromatography of the reaction mixture, was neutral and analysed for $C_{30}H_{29}NO_9$. The N.M.R. spectrum is reproduced below, fig. 3 and shows only one aromatic proton at 6.3 δ attached to the

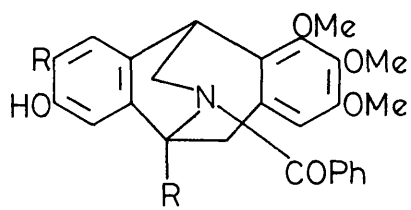
Fig. 3.



trimethoxybenzyl ring. This and the two aromatic singlets at 7.55 and 7.0 δ implies that a novel cyclisation to structure (87) or (88) has occurred. The salicylic ester methyl



(87)

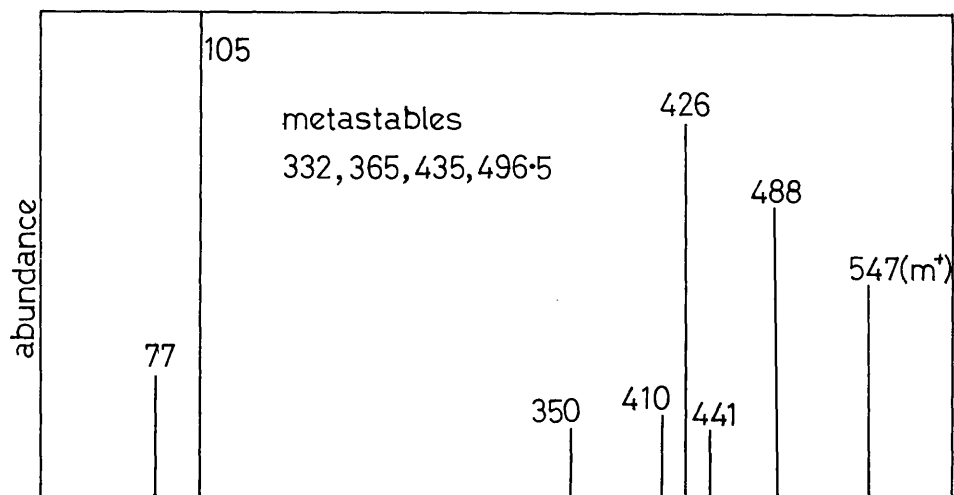


(88)

absorption appears at 3.84 δ whilst the tertiary ester absorption is at 3.55 δ . The mass spectrum is reproduced in histogram form in fig. 4 and is consistent with either the

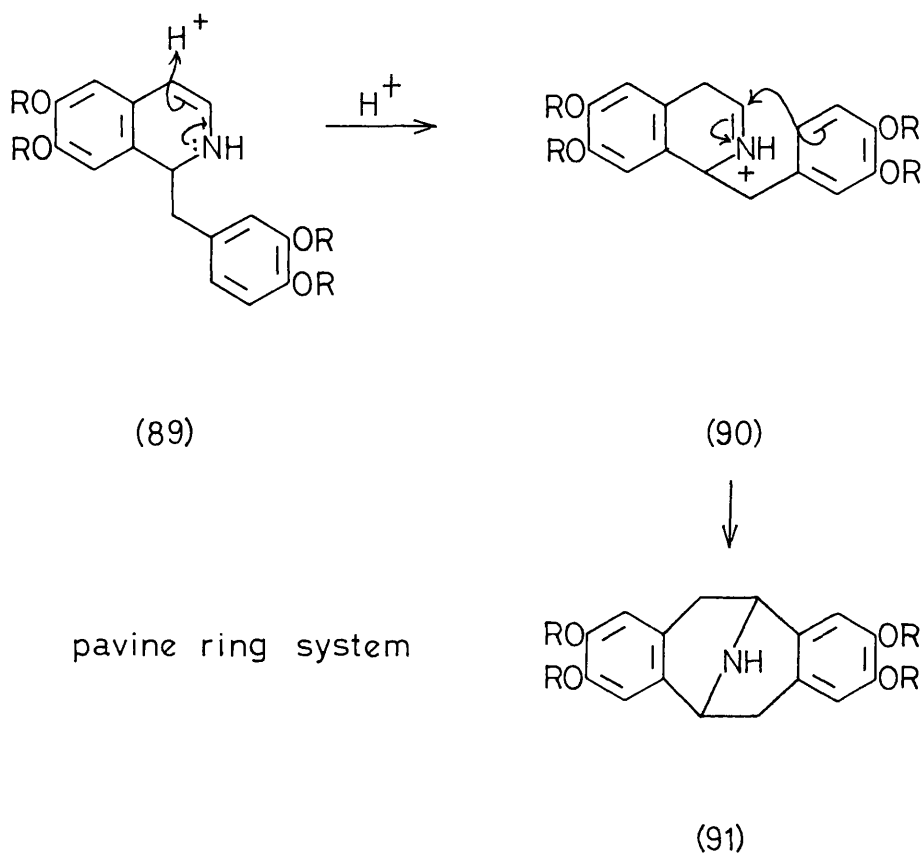
pavine structure (87) or the isopavine structure (88).

FIG 4



Before attempting to decide between structures (87) and (88) it is in order to discuss the mechanism of formation of the pavine ring system from 1-benzyl-1,2-dihydroisoquinolines of the type (89). This involves acid-catalysed cyclisation via nucleophilic attack at C_3 of the 1,4-dihydroisoquinolinium ion (90), which is formed by rapid protonation of the 1,2-dihydroisoquinoline⁵⁶.

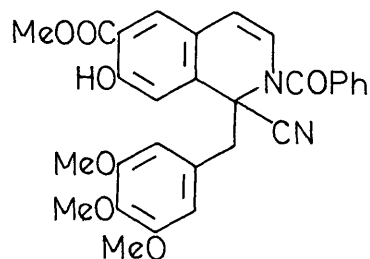
It has also been shown⁵⁷ that the reduction of aromatic isoquinoline derivatives with sodium borohydride proceeds through the 1,2-dihydroisoquinolinium intermediate with subsequent protonation at C_4 to produce the 1,4-dihydroisoquinolinium ion,



which reduces with ease to the 1,2,3,4-tetrahydro derivative. Reduction of 4-benzylisoquinolines with sodium borohydride often stops at the 1,2-dihydrostage and it has been suggested⁵⁷ that the system is stabilised by the alkyl substituent.

C_4 -Protonation of the enamide (75a) would be expected to

be difficult, in which case formation of the pavine system (87)



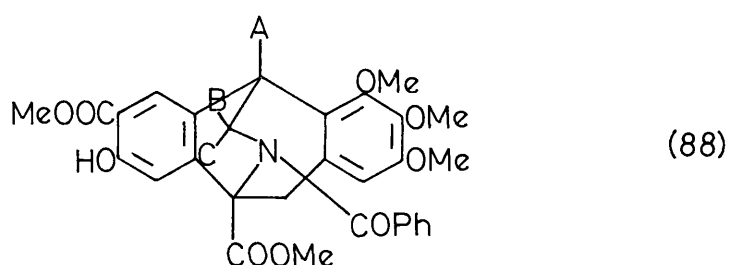
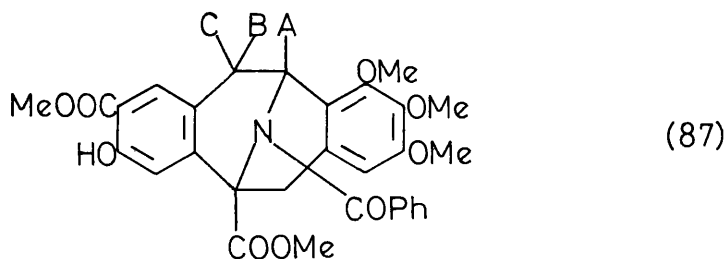
(75a)

would require the novel cyclisation of the activated trimethoxybenzyl ring to the styrene double bond, at C_3 . Alternatively the isopavine structure could arise by cyclisation to C_4 which would appear to be the more electrophilic of the two centres.

It is considered that incomplete conversion of the Reissert compound (75a) to the 1-benzylisoquinoline was achieved by the reaction of sodium methoxide in methanol. The ensuing treatment with hydrogen chloride caused ring closure of the benzyl group to either C_4 or C_3 , with concomitant or subsequent nitrile group methanolysis to give the pavine ring structure (87) or the isopavine system (88).

Further studies were made in order to assign a structure unequivocally to compound (X). Firstly a more detailed study of the N.M.R. spectrum was undertaken. Fig. 3 shows that

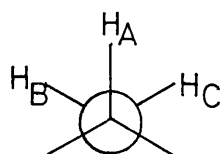
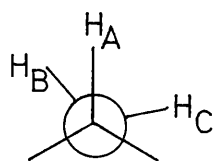
proton A absorbs as two doublets, one at 5.31δ and one at 5.40δ , each with a coupling constant of 1.6 Hz. Although



H_A in the pavine system (87) would be expected to absorb at a lower field than H_A in the isopavine system (88), chemical shift calculations would be unreliable because of possible shielding effects, both by the adjacent methoxy group^{58a,b} and the benzoyl group.

Fig. 5 shows the dihedral angles between protons H_A and H_B , and protons H_A and H_C as measured from molecular models of the two structures. From this the expected splitting patterns for both structures are constructed in Fig. 6, with the observed pattern for proton A.

FIG 5

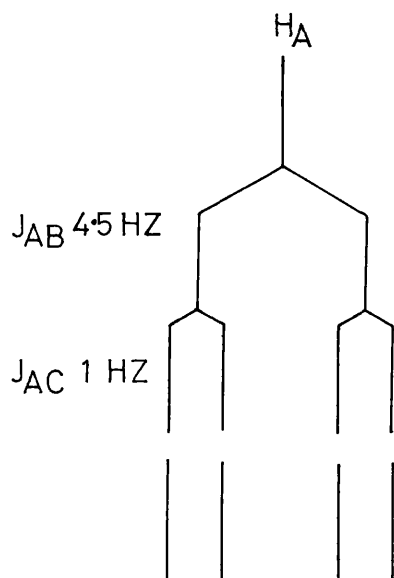


$$\angle H_A-H_B \approx 40^\circ$$

$$\angle H_A-H_B \approx \angle H_A-H_C$$

$$\angle H_A-H_C \approx 70^\circ$$

PAVINE (87)



ISOPAVINE (88)

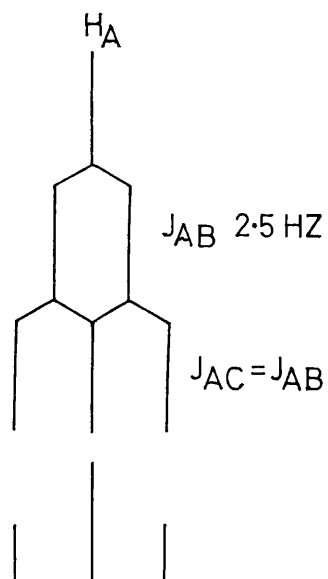
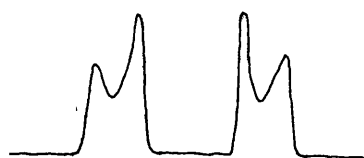
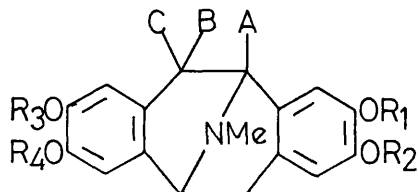


FIG 6

OBSERVED FOR (X)⁻

This supports the pavine structure (87) for X but is by no means conclusive. It is interesting to note that in pavine alkaloids of the general structure (91), proton A is observed to couple with H_B but not with H_C , such that it appears as a



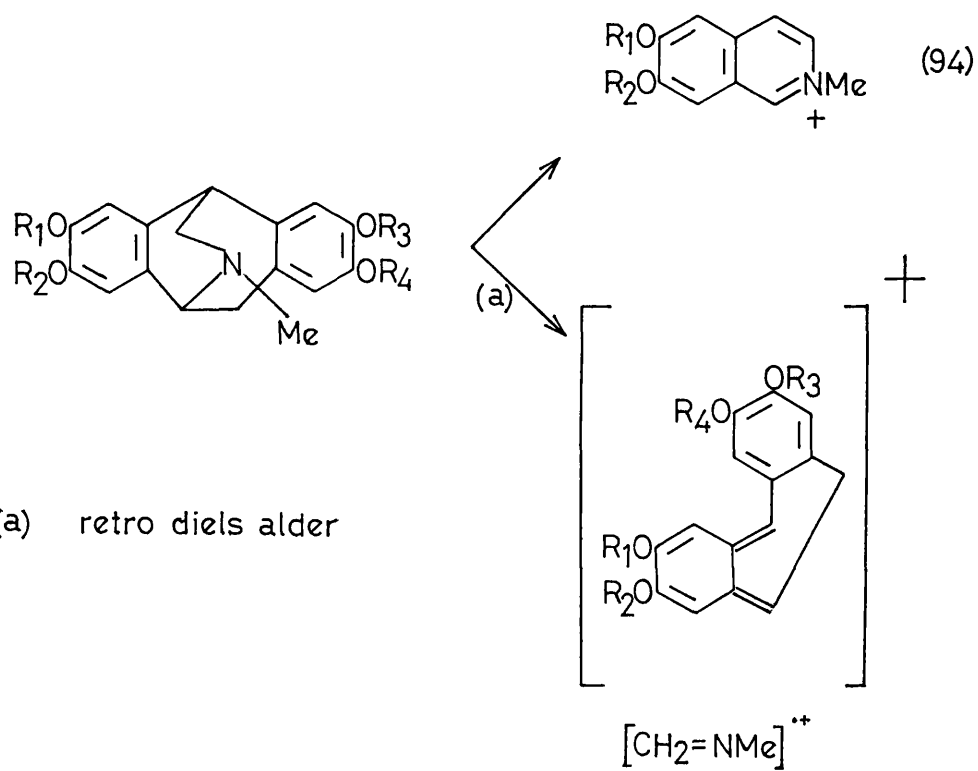
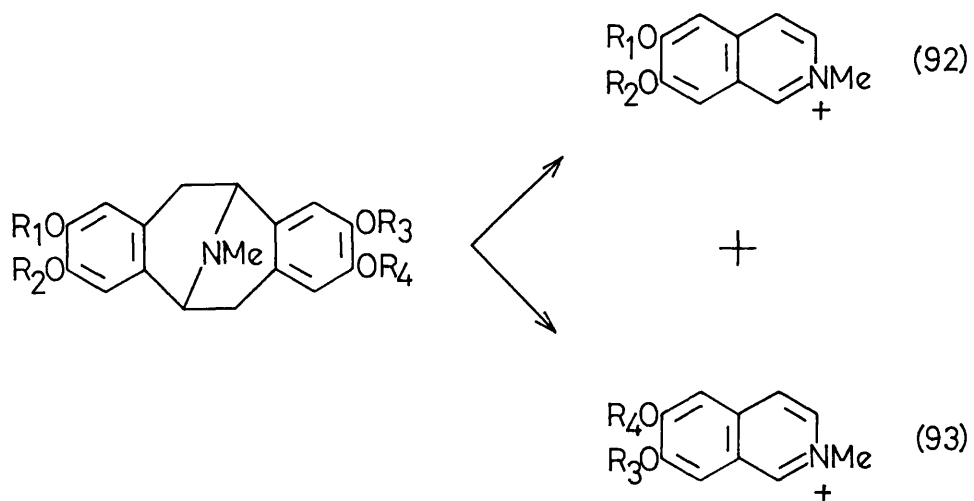
(91)

doublet with a coupling constant of 6.0 Hz ⁵⁹.

The remainder of the N.M.R. spectrum of (X) does not help to solve this problem so attention is turned to the M.S. The fragmentations of alkaloids based on the pavine and isopavine skeletons are known⁶⁰ and characteristic (Scheme 4) and the main differences between the two ring systems are:-

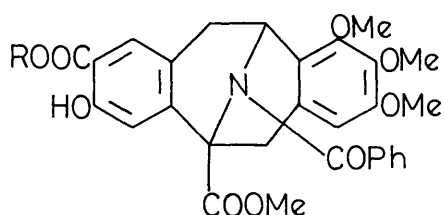
- (a) The presence of $M^+ - 43$, corresponding to the bridge loss of $\text{CH}_2 = \text{NMe}$ in the isopavine series only.
- (b) The presence, as base peaks, of the two isoquinolinium ions (92) and (93) in the pavine series and the one corresponding ion (94) in the isopavine series.

Scheme 4.



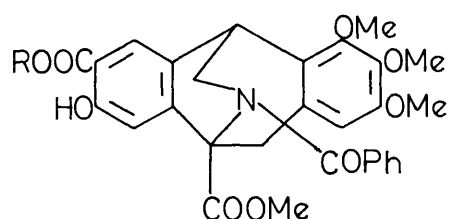
(a) retro diels alder

However, structures (87) and (88) contain several carbonyl groups which seem to alter the mass spectrum observed, which shows ($M^+ - \text{COOCH}_3$), and a strong peak at $m/e 426$ corresponding to a loss of PhCONH_2 from the molecular ion. This fragmentation is consistent with both of the postulated structures so it was reasoned that hydrolysis of the amide (X) would generate the methylamine bridge necessary to distinguish between (87) and (88).



(87) R = Me

(95) R = H

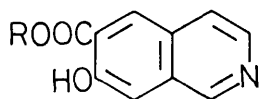


(88) R = Me

(96) R = H

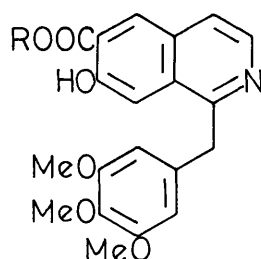
Treatment of the unknown compound with orthophosphoric acid⁶¹ at 110° afforded benzoic acid as a sublimate, but unfortunately no other pure material could be isolated from the reaction mixture.

A second degradative attempt involved treatment of (X) with 30% sodium hydroxide at 90° and afforded a solid product which showed an I.R. spectrum very similar to that of the starting material but which was an acidic substance. The N.M.R. spectrum showed the loss of the salicylic ester methyl absorption, and a high resolution mass measurement of the molecular ion confirmed the constitution of $C_{29}H_{27}NO_9$. An analogous M.S. breakdown to that of (X) was observed and on this basis the salicylic acid structures (95) or (96) were proposed. The U.V. spectrum showed an absorption maximum at 312nm which remained virtually unchanged on the addition of sodium hydroxide, whereas an absorption maximum of 322nm in the spectrum of (X) shifts to 350nm with base. A similar U.V. spectral phenomenon has been noted to exist between the acid-ester analogues (77) and (61) and (79) and (78) and is probably a reflection of the strong intramolecular hydrogen bonding in the salicylic acid derivatives.



(61) R=Me

(77) R=H

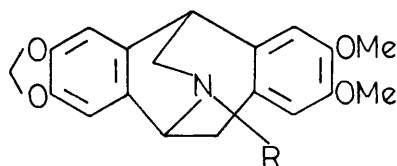


(78) R=Me

(79) R=H

Attempts to further degrade (95) or (96) involved the use of sodium ethoxide in ethanol. This, however, afforded only small quantities of starting material.

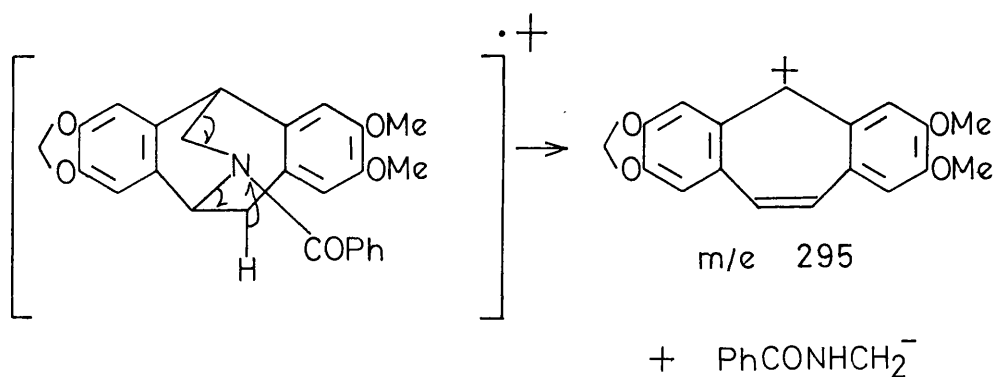
Evidence against the isopavine structure (88) for X was given by the mass spectral fragmentation of the N-benzoylisopavine (97), which was prepared from nor-amurensinine (98)⁶³. The spectrum exhibited a molecular ion at m/e 519 and a peak at



(97) $R = \text{COPh}$

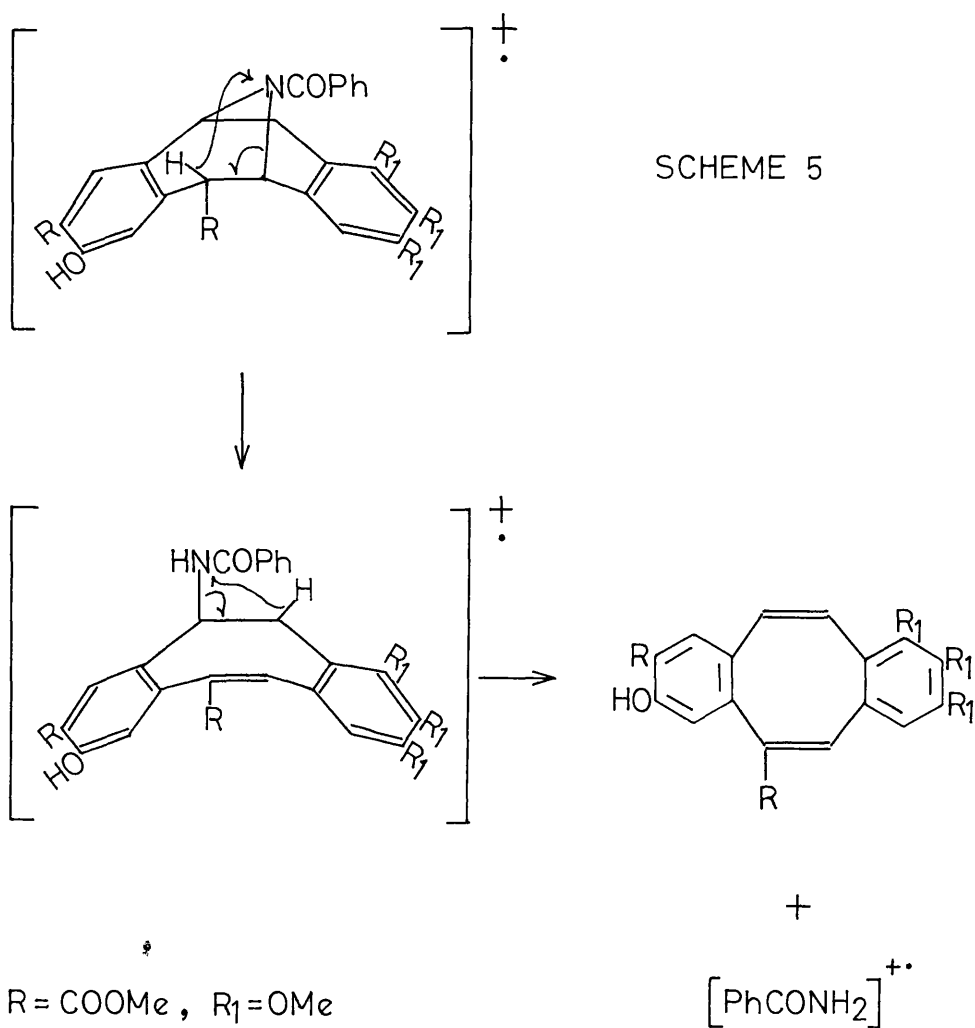
(98) $R = \text{H}$

m/e 295 which represented 90% of the base peak. m/e 295 corresponds to the loss of m/e 134 from the molecular ion and is considered to arise by such a mechanism as shown below. The



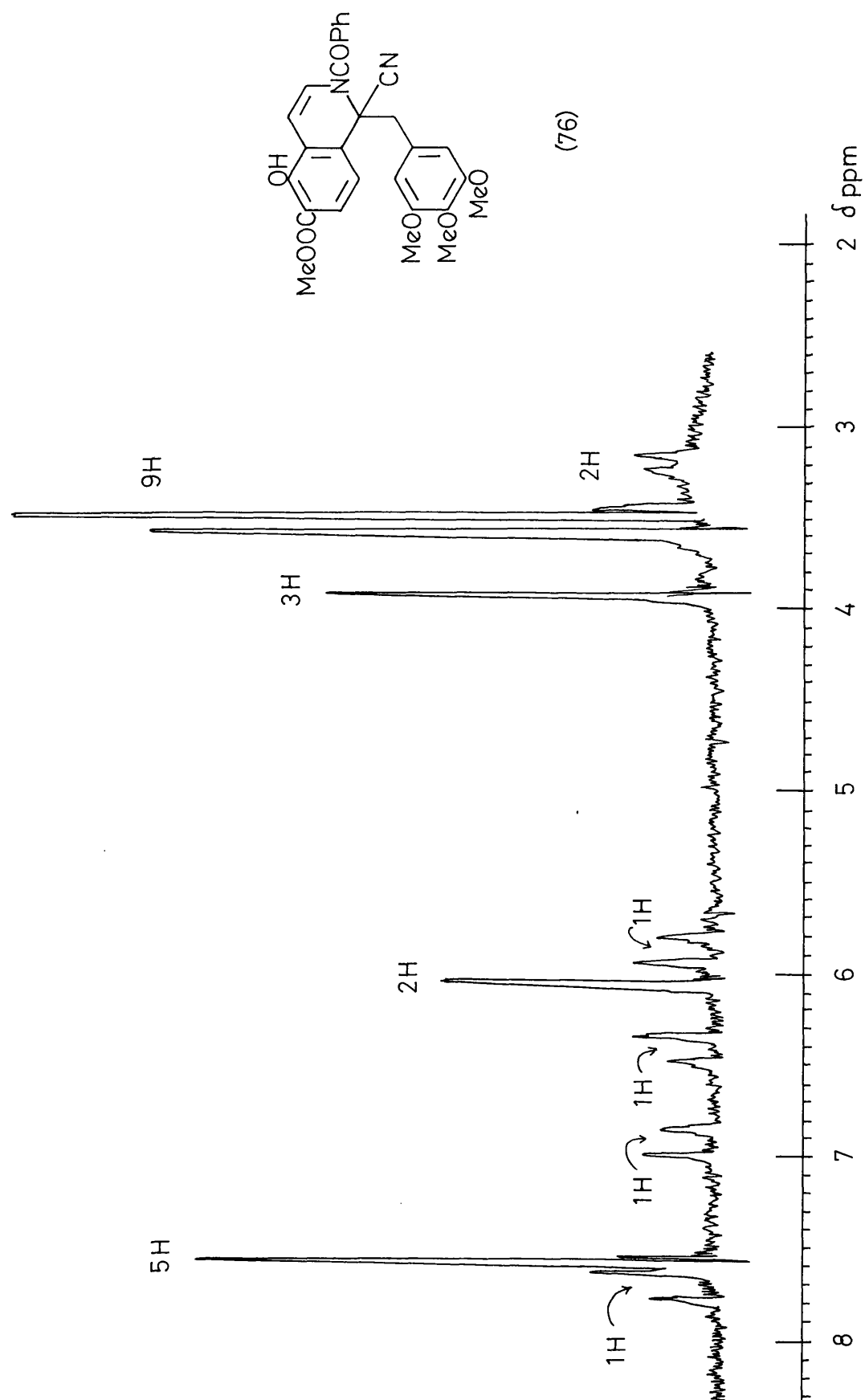
loss of m/e 121 (PhCONH_2) observed in the spectrum of compound X is evident only to the extent of 1% of the base peak.

It is suggested therefore that the pavine structure (89) is favoured for X. The bridge cleavage observed is rationalised by such a mechanism as shown in scheme 5, in which proton capture on nitrogen explains the formation of benzamide.

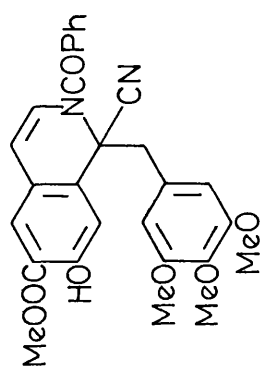


It is interesting to continue this thesis by looking at such tetracyclic systems as they occur in nature as isopavine alkaloids. Chapter 2 includes a brief review of isopavine chemistry and the author's contribution to the synthetic methods available for the synthesis of this ring system.

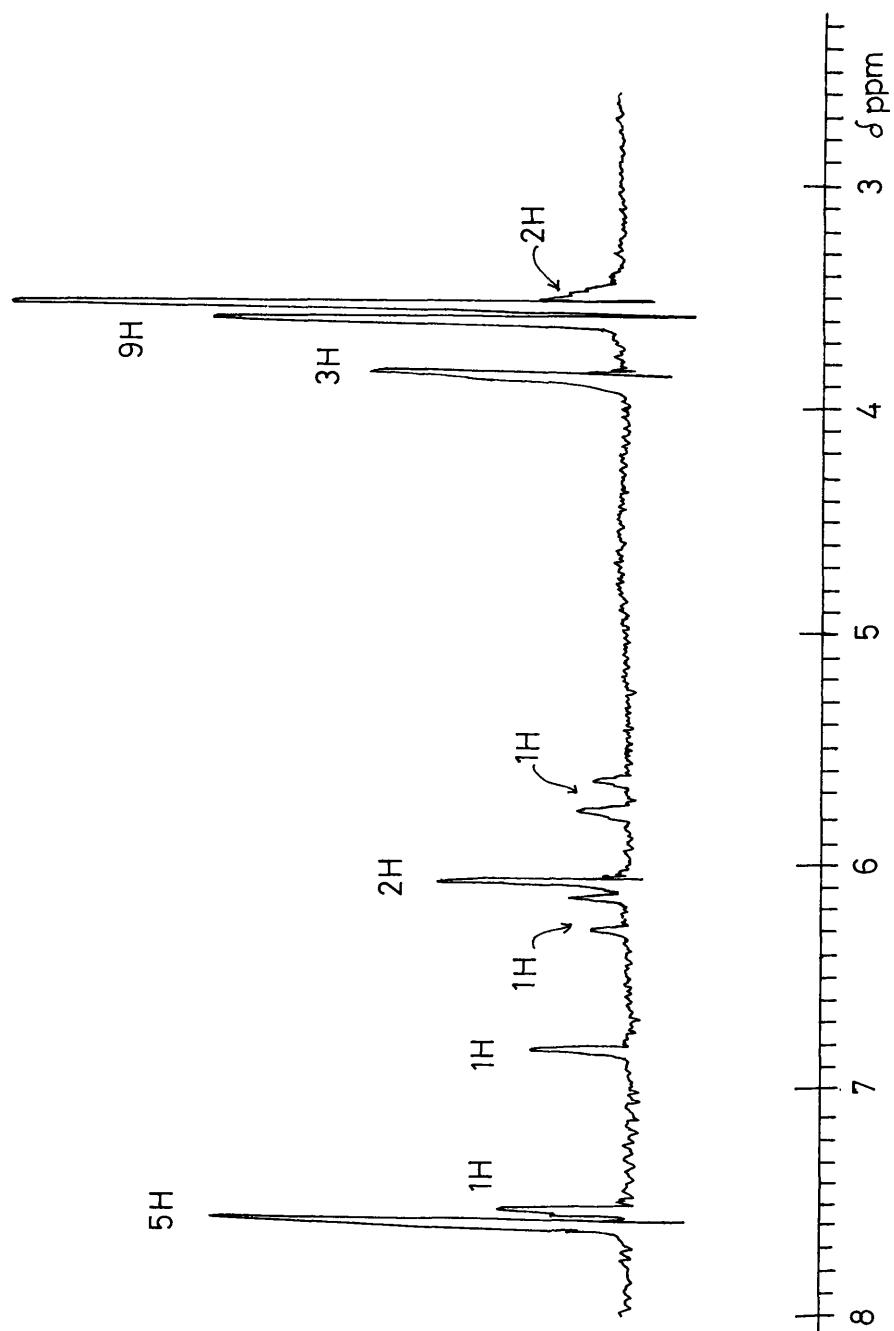
4. SPECTRA

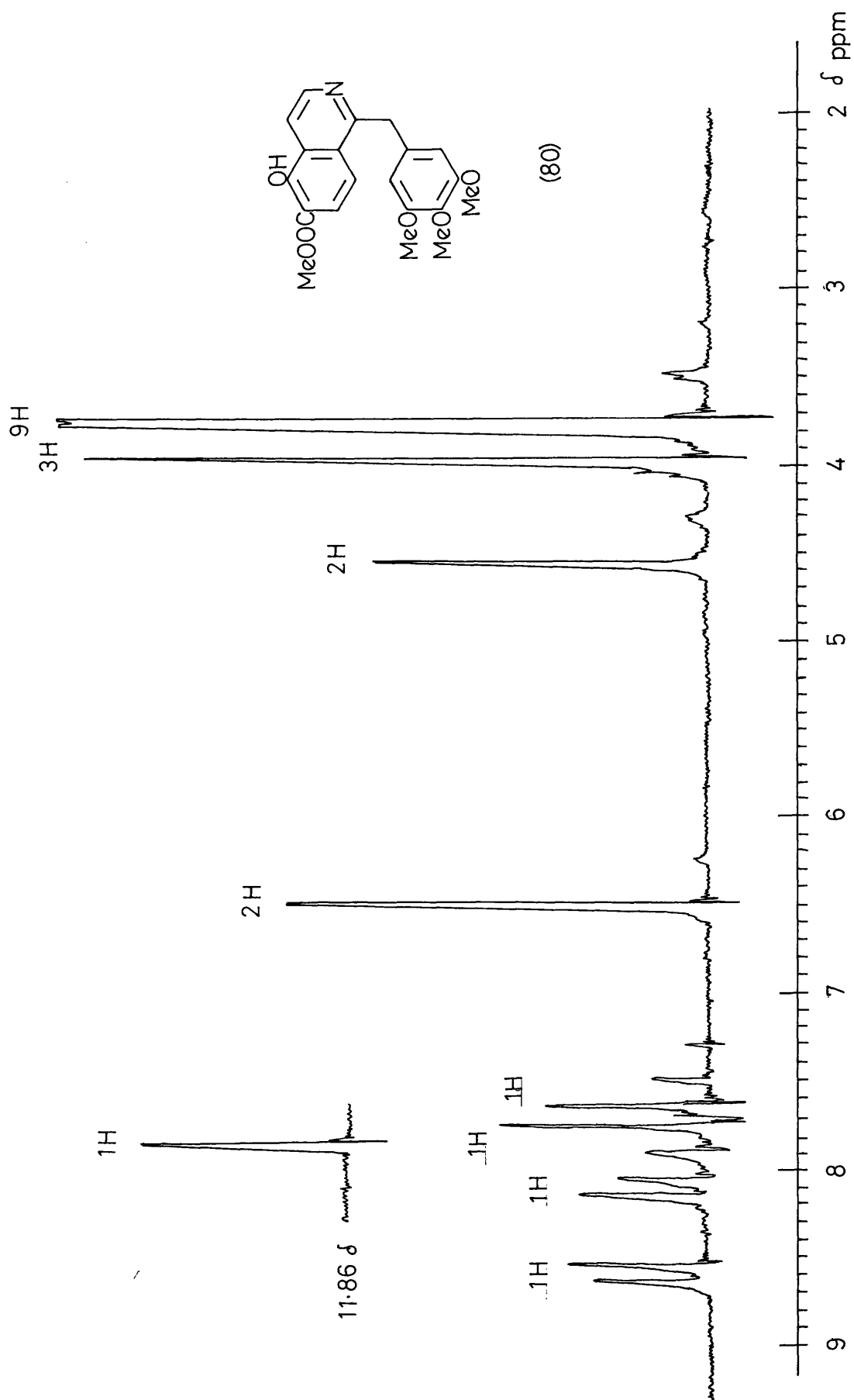


67a

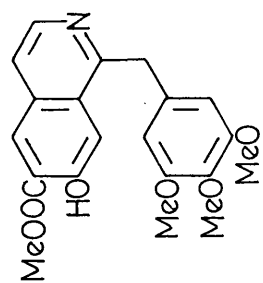


(75a)

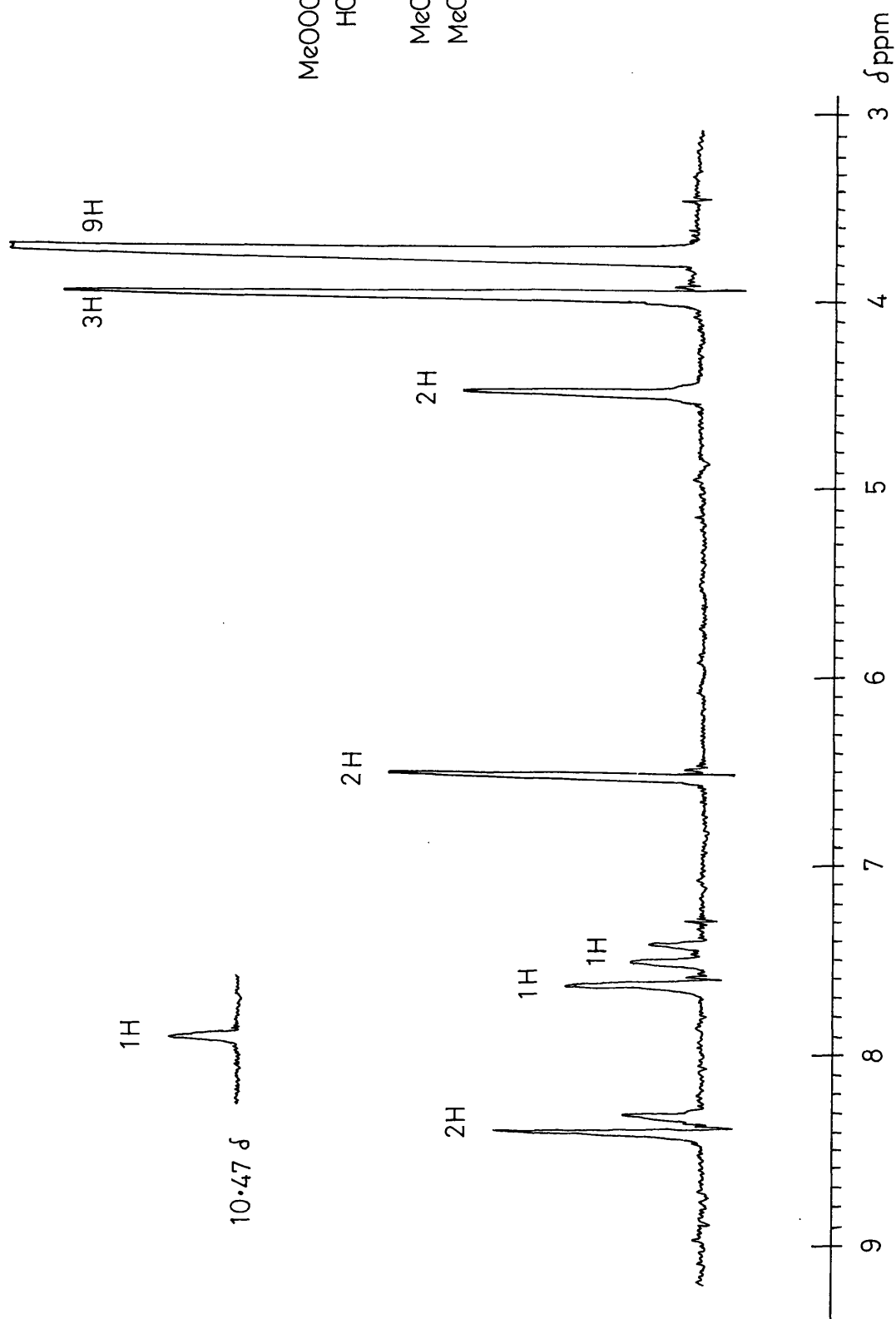




68a



(78)



5. EXPERIMENTAL

Methyl 2-acetoxy-4-methylbenzoate (44)

This was prepared in 70% yield based on metacresotinic acid (42) (100g) by formation of the methyl ester (101g) in hot MeOH(600ml) and HCl gas for 6 hr, isolation and subsequent treatment of the product (66.6g) in acetic anhydride (90ml) at steam bath temperature for 6 hours. The excess acetic anhydride was carefully decomposed with water and the product extracted into CHCl_3 ; b.pt 120° at 2.5 Torr, N.M.R. (CDCl_3) 8.0 d[1] $J=8.0\text{Hz}$ ($\text{C}_6\text{-H}$), 7.13 d[1] $J=8.0\text{Hz}$ ($\text{C}_5\text{-H}$), 6.96 s [1] ($\text{C}_3\text{-H}$), 3.88 s [3] (COOCH_3), 2.35 s [3] and 2.4 s [3] (Ar-CH_3 and Ar-OCOCH_3); ν_{max} (liquid film) 1776, 1727; λ_{max} 241 (17,700), 275 (1,100), 282 (935), 305 (450).

Methyl 2-acetoxy-4-(diacetoxymethyl)benzoate (45).

Glacial AcOH (500ml) was added to a soln. of CrO_3 (90g) in Ac_2O (750ml), the soln. was cooled to 0° and concentrated H_2SO_4 (50ml) added cautiously. This mixture was added dropwise over 4hr. to a stirred soln. of (44) (50g) in Ac_2O (500ml) maintained between -10° and -15° . After stirring for a further 2hr. the soln was allowed to reach 0° over 1 hr, and isopropanol (600ml) cautiously added, keeping the temperature below 15° . The resulting dark green soln. was evaporated to low bulk under reduced pressure at 35° and ice (500g) was added. The soln. was left for 1hr, then extracted with CHCl_3 (4x100ml). The combined CHCl_3 extracts were washed with saturated NaHCO_3 aq, and water and dried (MgSO_4). Removal of the CHCl_3 afforded a golden oil which solidified on standing (42g, 54%). Recrystallisation from MeOH afforded white crystals, m.p. 95° ; N.M.R. (CDCl_3),

8.01 d [1] $J=8.7\text{Hz}$ ($\text{C}_6\text{-H}$), 7.68 s [1] (Ar-CH), 7.4 d [1] $J=8.7\text{Hz}$ ($\text{C}_5\text{-H}$), 7.26 s [1] ($\text{C}_3\text{-H}$), 3.83 s [3] (COOCH_3), 2.3 s [3] (Ar-O-COCH_3), 2.1 s [6] (OCOCH_3)₂; ν_{max} , 1765 broad, 1710, 1628; λ_{max} (ϵ), 283 (1,100), 232 (13,000). (Found: C, 55.7; H, 4.9. $\text{C}_{15}\text{H}_{16}\text{O}_8$ requires: C, 55.6; H, 5.0%).

Isolation of methyl 2-acetoxy-4-carboxybenzoate (46).

The combined NaHCO_3 washings from the previous experiment were acidified with 2N HCl, and the soln. extracted with CHCl_3 (3x100ml). The combined extracts were washed (brine) dried (MgSO_4) and evaporated to give a white solid, (5%) m.p. $185-6^\circ$ (MeOH). N.M.R. (DMSO) 13.5-11.0 broad s [1] (COOH , removed by D_2O), 7.7-7.2 complex [3] (aromatic H), 3.86 s [3] (ArCOOCH_3), 2.32 s [3] (ArOCOCH_3); ν_{max} 3300-2300, 1770, 1715, 1690; λ_{max} (ϵ) 294 (2100), 240 (16,300). (Found: C, 55.3; H, 4.1. $\text{C}_{11}\text{H}_{10}\text{O}_6$ requires: C, 55.5; H, 4.2%).

Methyl 2-acetoxy-4-formylbenzoate (47).

The aldehyde triacetate (45) (25.6g) was heated on a steam bath for 3hr. in glacial AcOH (250ml) and conc. HCl (5ml). CHCl_3 (200ml) was added to the cooled soln. and the reaction mixture washed with NaHCO_3 , brine and dried (MgSO_4). Removal of the solvent afforded a yellow oil which crystallised on standing (80%). Recrystallisation from petrol/benzene afforded (47) as colourless florets, m.p. $79-80^\circ$, N.M.R. (CDCl_3) 9.98 s [1] (CHO), 8.09 d [1] $J=8.0\text{ Hz}$ ($\text{C}_6\text{-H}$), 7.74 d [1] $J=8.0\text{ Hz}$ ($\text{C}_5\text{-H}$), 7.57 d [1] $J=1.7\text{Hz}$ ($\text{C}_3\text{-H}$); ν_{max} 1763, 1726, 1703, 1573. (Found: C, 59.5; H, 4.5. $\text{C}_{11}\text{H}_{10}\text{O}_5$ requires: C, 59.3; H, 4.5%).

Methyl 2-acetoxy-4 (2,2-dimethoxyethoxy)imino methyl benzoate (48)

A mixture of the aldehyde (4.2g) (47) and excess aminoacetaldehyde-dimethylacetal (5ml) in benzene (200ml) was heated under reflux for 8 hr. The solid product obtained after removal of the solvent was recrystallised from petrol (3.7g) (60%). N.M.R. (CDCl_3) 8.3 s [1] ($\text{CH}=\text{N}-$), 8.0-7.25 complex [3] (aromatic H), 4.0-3.7 m [2] ($\text{CH}_2-\text{CH}(\text{OCH}_3)_2$), 4.36 t [1] $J=5.2\text{Hz}$ ($\text{CH}_2-\text{CH}(\text{OCH}_3)_2$), 3.86 s [3] (COOCH_3), 3.36 s [6] ($\text{CH}_2\text{CH}-(\text{OCH}_3)_2$), 1.93 s [3] (OCOCH_3); ν_{max} 1770, 1720, 1650.

Methyl 4-formyl-2-hydroxybenzoate (49).

The aldehyde triacetate (45) (42.0g) was heated under reflux with MeOH (300ml) and H_2SO_4 (10ml; 98%) for 3 hr. After removal of the MeOH under reduced pressure, ice (200g) was added and the soln. extracted with CHCl_3 (4x100ml). The combined CHCl_3 extracts were washed with NaHCO_3 (3x100ml), water (2x100ml) and dried (MgSO_4). Removal of the solvent afforded a solid which recrystallised as white florets from 60-80 petrol (23.4g, 85%) m.p. 76-77°; N.M.R. (CDCl_3), 10.82 s [1] ($-\text{OH}$, removed by D_2O), 10.01 s [1] ($-\text{CHO}$), 7.98 d [1] $J=8.0\text{Hz}$ (C_5-H), 7.36 d [1] $J=8.0\text{Hz}$ (C_6-H), 7.43 s [1] (C_2-H), 3.96 s [3] ($-\text{COOCH}_3$); ν_{max} , 3250, 1700 broad, 1625, 1580; λ_{max} (ϵ), 340 (3,200), 264 sh (11,300), 258 (12,00), 250 (10,600). (Found: C, 59.9; H, 4.5. $\text{C}_9\text{H}_8\text{O}_4$ requires: C, 60.0; H, 4.5%).

Methyl 4-[(2,2-dimethoxyethyl)imino]methyl]-2-hydroxybenzoate (50)

A mixture of methyl 4-formyl-2-hydroxy benzoate (60g) and aminoacetaldehydedimethylacetal (35g) in benzene (500ml) was heated under reflux for 4 hr. The solid product obtained after removal of the solvent was recrystallised from petrol (60-80), (80g, 90%), m.p. 64-65°; N.M.R. (CDCl_3), 10.77 s [1] (-OH, removed by D_2O), 8.0-7.2 complex [3] (Aromatic H), 8.25 s [1] (Ar-CH=N-), 4.70 t [1] $J=5.0$ Hz (-CH-(OMe)₂), 3.93 s [3] (COOCH₃), 3.42 s [6] (2xOCH₃), 3.7-3.9 m [2] (N-CH₂-CH-); ν_{max} , 3130, 1680, 1652, 1623; λ_{max} (ϵ), 334 (4,600), 265 (22,800), 272 sh (20,000). (Found: C, 58.4; H, 6.4; N, 5.3. $\text{C}_{13}\text{H}_{17}\text{NO}_5$ requires: C, 58.4; H, 6.4; N, 5.3%).

Methyl 4-[(2,2-dimethoxyethyl)amino]methyl]-2-hydroxybenzoate (53).

Catalytic reduction of the Schiff's base (50) in EtOH, using 10% Pd/C at 45 lb/sq. in. for 3 hr gave a yellow oil. N.M.R. (CCl_4) 7.69 d [1] $J=8.0$ Hz ($\text{C}_6\text{-H}$), 6.65 complex [2] ($\text{C}_5\text{-H}$ and $\text{C}_3\text{-H}$), 4.38 t [1] $J=5.5$ Hz ($\text{CH}_2\text{CH}(\text{OCH}_3)_2$), 3.90 s [3] (COOCH₃), 3.71 s [2] (ArCH₂-NC), 3.29 s [6] ($\text{CH}_2\text{CH}(\text{OCH}_3)_2$), 2.61 d [2] $J=5.5$ Hz ($\text{CH}_2\text{CH}(\text{OCH}_3)_2$). The hydrochloride salt was obtained as white needles from C_6H_6 (90%) m.p. 163-4°; ν_{max} 3160, 2800-2400 (several bands), 1665; λ_{max} (ϵ) 312 (4,600), 242 (10,800). (Found: C, 51.3; H, 6.8; N, 4.6. $\text{C}_{12}\text{H}_{20}\text{NO}_5\text{HCl}$ requires: C, 51.0; H, 6.6; N, 4.6%).

Cyclisation of the acetal (53) in the presence of veratraldehyde.

The acetal (53) (270mg) was heated under reflux with veratraldehyde (100mg) in 6N methanolic HCl for 1 hr. On cooling to 0° an orange solid separated (20mg) ν_{max} 3500-2500, 1680, 1630; λ_{max} 335 (broad) mass m/e 353 (M^+) [100%], 321 [30%].

Attempted cyclisation of the acetal (53) with BF_3 .

Gaseous BF_3 was passed through a soln. of (53) (500mg) in CH_2Cl_2 (12ml). NaOH (15%, 10ml) was added and the mixture stirred at R.T. for 20hr. The soln. was acidified (HCl), rebasified (NaHCO_3) and extracted into ether. The combined ether extracts were washed (H_2O), dried (MgSO_4) and evaporated to afford a reddish solid (120mg) m.p. $100-115^\circ$, mass m/e 269 (low ev). TLC on alumina showed several components and further purification proved impossible.

Methyl 4-[(2,2-dimethoxyethyl)p-toluenesulphonamido]methyl]-2-hydroxybenzoate (58).

The acetal (53) (4.0g) was heated on a steam bath with pyridine (100ml) and tosyl chloride (5.6g) for 1.5 hr. After removal of the solvent, the residue was dissolved in CHCl_3 (50ml) washed (NaHCO_3 and H_2O) dried (MgSO_4) and evaporated to yield a pale red oil which crystallised from petrol (60-80) as lemon plates (3.8g, 60%) m.p. 93° , N.M.R. (CDCl_3) 7.85-6.6 complex [7] (aromatic H), 4.40 s [2] ($\text{Ar}-\text{CH}_2-\text{N}<$), 4.3 t [1] $J=5.0 \text{ Hz}$ ($\text{CH}_2-\text{CH}-(\text{OCH}_3)_2$), 3.87 s [3] (COOCH_3), 3.28 d [2] ($\text{CH}_2-\text{CH}-(\text{OCH}_3)_2$), 3.17 s [6] ($\text{CH}_2-\text{CH}-(\text{OCH}_3)_2$), 2.38 s [3] ($\text{Ar}-\text{CH}_3$); ν_{max} 3170, 1670, 1345, 1168 ; λ_{max} (ϵ) 310 (4000), 243 (15,000); mass m/e 423 (M^+) [1.5%] , 268 [100%] . (Found: C, 56.9; H, 6.0; N, 3.3; S, 7.8. $\text{C}_{20}\text{H}_{25}\text{NSO}_7$ requires: C, 56.7; H, 5.9; N, 3.3; S, 7.6%).

Methyl 4-[[[(2,2-dimethoxyethyl)benzene sulphonamido]methyl]-2-hydroxy benzoate was prepared (62%) by the same procedure as above. The product was an oil which resisted crystallisation, N.M.R. (CDCl_3) 7.9-6.7 complex [8] (aromatic H), 4.46 s [2] ($\text{Ar-CH}_2\text{-N}$), 4.35 t [1] $J=5.0$ Hz ($\text{CH}_2\text{-CH-(OCH}_3)_2$), 3.90 s [3] (COOCH_3), 3.24-3.15 complex [8] ($\text{CH}_2\text{-CH-(OCH}_3)_2$); ν_{max} (oil film) 3500, 1678, 1440, 1340, 1155; λ_{max} (ξ) 310 (3600), 242 (12000); mass m/e 409 (M^+) [0.5%], 268 [100%].

Methyl 1,2-dihydro-7-hydroxy-2-p-toluenesulphonylisoquinoline-6-carboxylate (59)

The tosyl acetal (58) (2.0g) was heated under reflux in 6N methanolic HCl for 40 hr. A yellow powder was collected on cooling to 0° (0.92g, 64%) m.p. $191-3^\circ$, this product could not be recrystallised or sublimed. N.M.R. ($\text{CDCl}_3/\text{DMSO}$) 7.9-7.2 complex [5] (aromatic H), 6.80 s [1] ($\text{C}_8\text{-H}$), 6.68 d [1] $J=8.0$ Hz ($\text{C}_3\text{-H}$), 5.93 d [1] $J=8.0$ Hz ($\text{C}_4\text{-H}$), 4.51 s [2] ($\text{Ar-CH}_2\text{-N}$), 3.84 s [3] (COOCH_3), 2.34 s [3] (Ar-CH_3); ν_{max} 3130, 1690, 1625, 1280, 1175; λ_{max} (ξ) 298 (8300), 235 (24000); mass m/e 359 (M^+) [30%], 204 [75%], 172 [100%], 116 [33%]; (M^+ found: 359.0835; $\text{C}_{18}\text{H}_{17}\text{NO}_5\text{S}$ requires 359.0828).

Attempts to remove the tosyl function from the N-tosyl-1,2-dihydro-
isoquinoline (59). All of these reactions returned starting material.

METHOD (UNDER N₂)

NaOMe/dry MeOH at reflux 1hr.

Ktbutoxide/dry-t-butanol at reflux 1 hr.

K.t butoxide/dry-t-butanol/DMF at reflux 4hr.

Pd/C/toluene at reflux 1 hr.

Pd/C used at 200° 15 min

Reduction of the N-tosyl-1,2-dihydroisoquinoline (59).

(59) (207mg) was hydrogenated in glacial AcOH (60ml) using 10% Pd/C at 45 lb/sq. in. at 40° for 20hr. Removal of the catalyst and solvent and trituration of the residue with NaHCO₃ soln. afforded a yellow solid (70mg) m.p. 95-100°; N.M.R. (CDCl₃) 7.9-6.6 complex [6] (aromatic H), 4.5-4.2 complex and 3.8-3.2 complex (6xaliphatic H), 3.9 s [3] (COOCH₃); ν_{\max} 1678, 1340, 1160, 1085; λ_{\max} 309; mass m/e 361 [M⁺] (18%).

Isolation of diphenyldisulphone (69).

KCN (6.2g) in H_2O (16ml) was added to a soln. of the Schiff's base (50) (7.6g) in CH_2Cl_2 (40ml). Benzenesulphonyl chloride (106g) was added dropwise in CH_2Cl_2 (30ml) over 1 hr. The reaction was stirred for 6 days, the two phases separated and the aqueous layer washed with CH_2Cl_2 . The combined organic extracts were washed with H_2O , 2N HCl, 2N NaOH and water. After drying (MgSO_4), the soln was evaporated to give a red oil which on trituration with EtOH gave diphenyldisulphone (69) (1.0g). Recrystallisation from MeOH afforded white needles m.p. $189-90^\circ$ N.M.R. (DMSO) 8.1-7.5 symmetrical complex (aromatic H); ν_{max} 1580, 1345, 1330, 1305, 1140, 1048, 742, 700; λ_{max} (ϵ) 240 (11,000); mass m/e 282 (M^+) [1.2%], 234, 141 [81%], 77 [100%]. (Found: C, 51.2; H, 3.3; S, 22.9. $\text{C}_{12}\text{H}_{10}\text{S}_2\text{O}_4$ requires: C, 51.1; H, 3.54; S, 22.7%).

Attempted oxidation of (44) with ceric ammonium nitrile (C.A.N.)

The benzoate derivative (44) (205mg) was added to C.A.N. (4.1g) in glacial AcOH (8ml) and H_2O (8ml) and heated on a steam bath for 1.5hr. The solvent was removed under reduced pressure and the residue digested with H_2O and extracted into ether (4 x 40ml). The combined etherial layer was washed with H_2O , dried (MgSO_4) and evaporated to give a yellow solid (0.38g) ν_{max} 3200-2500, 1685, 1550 strong, 1350 strong. P.L.C. over silica eluted with C_6H_6 afforded at R_f 0.1, methyl-3,5-dinitro-2-hydroxy-4-methylbenzoate (51) (120mg, 39%), m.p. $110-114^\circ$.

N.M.R. (DMSO) 8.63 s [1] (Ar-H), 3.5 broad s [1] (-OH, removed by D₂O), 3.38 s [3] (COOCH₃), 1.91 s [3] (ArCH₃); ν_{\max} 3550 sharp, 3500-3000, 1695, 1545, 1340, 800; $\lambda_{\max}(\epsilon)$ 340 sh (5660), 378 (6320). mass m/e 256 (M⁺) [100%], 238 [21%], 239 [7%], 224 [60%], 207 [95%] metastable 191.5.

Methyl 2-hydroxy-4-methyl-5-nitrobenzoate (52) (100mg) (40%) was also obtained (Rf 0.6) as white needles from petrol m.p. 73-4°.

N.M.R. (CDCl₃) 11.5 broad s [1] (OH, removed by D₂O), 8.64 s [1] (C₆-H), 6.92 s [1] (C₃-H), 4.03 s [3] (COOCH₃), 2.66 s [3] (Ar-CH₃); ν_{\max} (soln in CHCl₃) 3400-3000, 1670, 1595, 1525, 1330; $\lambda_{\max}(\epsilon)$ 300 (6,600), 234 (17,400), λ_{\max} in EtOH/NaOH 280, 335, 394; mass m/e 211 (M⁺) [100%], 194 [90%], 179 [88%], 162 [40%] metastable 146.5 (Found: C, 51.4; H, 4.3; N, 6.6. C₉H₉NO₅ requires: C, 51.2; H, 4.3; N, 6.6%).

CYCLISATION OF SCHIFFS BASE (50)					Ratio of Isoquinolines	
Reaction conditions		Reaction time (hr)	Crude Yield Isoquinolines	Recovered Schiff's base or Aldehyde	(71)	(61)
Reagent	Temp °			**		
				*		
H ₂ SO ₄ 98% w/w	20	20	30%	* 60%	3	5
H ₂ SO ₄ 86% w/w	20	20	40%	* 55%	1	1
H ₂ SO ₄ 76% w/w	20	168	45%	* 45%	1	3
P.P.A.	20	24	Poor	** 90%	1	3
P.P.A.	45	24	40%	** 20%	1	2
P.P.A.	50	24	60%	** 15%	1	1
P.P.A.	70-100	5	95%	0%	3	1
H ₃ PO ₄ (SG 1.75)	35	24	Poor	86% *		
H ₃ PO ₄ (SG 1.75)	70-90°	1	Poor	80% *		
P ₂ O ₅ /pyridine	reflux	2	Poor	50% **		
P.P.E.	40	72	Nil	Some aldehyde at 40°		
P.P.E.	100	2	Nil	But unidentified basic material		

Methyl 7-hydroxyisoquinoline-6-carboxylate (61) and
methyl 5-hydroxyisoquinoline-6-carboxylate (71) see Table

The Schiff's base (50) (12.0g) was stirred at 70-80° in freshly prepared polyphosphoric acid (orthophosphoric acid (90ml), P₂O₅ (120g) for 5hr. After dilution with water (1 litre) the soln was basified with NaHCO₃ and extracted with CHCl₃ (4 x 150ml). The combined CHCl₃ extracts were washed with water (2 x 100ml), dried (MgSO₄) and evaporated to leave a yellow solid (8.6g, 94%).

Chromatographic separation of 200mg on silica, eluting with C₆H₆/CHCl₃ (50:50) afforded methyl 7-hydroxyisoquinoline-6-carboxylate (61) 40 mg, m.p. 120-121°; N.M.R. (CDCl₃) 9.1 s [1] (C₁-H), 8.36 d [1] J=6.0 Hz (C₃-H), 7.49 d [1] J=6.0 Hz (C₄-H), 8.34 s [1] (C₅-H), 7.34 s [1] (C₈-H), 4.00 s [3] (COOCH₃); ν_{\max} (solution in CHCl₃), 3270, 1692, 1640, 1258; λ_{\max} (ϵ), 380 (2,860), 270 (5,700), 235 (51,800); mass m/e 203 (M⁺) [65%], 171 (100%). (Found: C, 64.9; H, 4.5; N, 7.0. C₁₁H₉NO₃ requires: C, 65.0; H, 4.5; N, 6.9%). Also from the chromatographic separation was obtained methyl 5-hydroxyisoquinoline-6-carboxylate (71) 120 mg m.p. 137-138°; N.M.R. (CDCl₃), 12.8 s [1] (-OH, removed by D₂O), 9.1 s broad [1] (C₁-H), 8.58 d broad [1] J=6 Hz (C₃-H), 8.05 d [1] J=6 Hz (C₄-H), 7.77 d [1] J=8.8 Hz (C₇-H), 7.28 d [1] J=8.8 Hz (C₈-H), 3.94 s [3] (COOCH₃); ν_{\max} (soln in CHCl₃), 2800-3520, 1676, 1642, 1260; λ_{\max} (ϵ), 365 (5,200), 351 (5,600), 275 sh (5000), 254 (25,000); mass m/e 203 (M⁺) [50%], 171 [100%]. (Found: C, 65.2; H, 4.6; N, 7.1. C₁₁H₉NO₃ requires C, 65.0; H, 4.5; N, 6.9%). Subsequently isomers (61) and (71) were separated by fractional crystallisation using either petrol (60-80) or EtOH.

Methyl 2-benzoyl-7-benzoyloxy-1-cyano-1,2-dihydroisoquinoline-6-carboxylate (73).

A mixture of (61) (10g), CH_2Cl_2 (60ml), KCN (16g) and water (30ml) was stirred whilst benzoyl chloride (28g) in CH_2Cl_2 (20ml) was added during 2hr. After stirring for a further 24hr the layers were separated and the CH_2Cl_2 layer washed with water, 2N HCl, water, 2N NaOH and water. The soln was dried (MgSO_4) and evaporated to give a red oil which crystallised from n-BuOH. Recrystallisation from MeOH gave white needles (5.5g, 24%) m.p. $203-3^\circ$; N.M.R. (DMSO), 8.3-7.4 complex [12] (Aromatic H), 7.04 s broad [1] ($\text{C}_1\text{-H}$), 6.83 d [1] $J=8.0\text{ Hz}$ ($\text{C}_3\text{-H}$), 6.33 d [1] $J=8.0\text{ Hz}$ ($\text{C}_4\text{-H}$), 3.70 s [3] (COOCH_3); ν_{max} , 1758, 1710, 1670, 1640, 1626; λ_{max} (ϵ), 330 sh (6,200), 291 (15,000), 239 (39,000); mass m/e 438 (M^+) [18%], 105 [100%] 338 [80%]. (Found: C, 71.0; H, 4.1; N, 6.3. $\text{C}_{26}\text{H}_{18}\text{N}_2\text{O}_5$ requires: C, 71.2; H, 4.1; N, 6.4%).

About 30% of the starting material was recovered as the O-benzoate (75) from the 2N HCl washings by basification (NaHCO_3) and extraction with CHCl_3 , and could be recycled. The hydrochloride salt was recrystallised from EtOH, m.p. $196-197^\circ$; N.M.R. (DMSO), 9.93 s [1] ($\text{C}_1\text{-H}$), 8.97 s [1] ($\text{C}_5\text{-H}$), 8.57 s [1] ($\text{C}_8\text{-H}$), 8.83 d [1] $J=6.0\text{ Hz}$ ($\text{C}_3\text{-H}$), 8.63 d [1] $J=6.0\text{ Hz}$ ($\text{C}_4\text{-H}$), 8.4-7.6 complex [5] ($\text{O-CO-C}_6\text{H}_5$), 3.86 s [3] (COOCH_3); ν_{max} , 2350-1960 several bands, 1740, 1721; λ_{max} (ϵ), 338 (2,900), 230 (61,600); mass m/e 307 (M^+) [25%], 105 [100%]. Found: C, 63.0; H, 4.0; N, 4.1; Cl, 10.0. $\text{C}_{18}\text{H}_{13}\text{NO}_4\text{HCl}$

requires: C, 62.9; H, 4.1; N, 4.1; Cl, 10.3%).

In an analogous experiment methyl 2-benzoyl-5-benzoyloxy-1-cyano-1,2-dihydroisoquinoline-6-carboxylate (74) was prepared (18%) from (71). It crystallised as white needles from MeOH, m.p. 194-195°; N.M.R. (DMSO), 8.4-7.4 complex [12] (Aromatic H), 7.15 s [1] (C₁-H), 6.86 d [1] J=8.0 Hz (C₃-H), 6.19 d [1] J=8.0 Hz (C₄-H), 3.7 s [1] (COOCH₃); ν_{\max} , 1740, 1680, 1635, 1603; λ_{\max} (ϵ), 330 sh (6,300), 293 (13,600), 238 (39,000); mass m/e 438 (M⁺) [8%], 105 [100%]. Found: C, 71.2; H, 4.1; N, 6.6. C₂₆H₁₈N₂O₅ requires: C, 71.2; H, 4.1; N, 6.4%.

Again, starting material was recovered in about 30% yield as O-benzoate (76) from the HCl washings and could be recycled. Methyl 5-benzoyloxyisoquinoline-6-carboxylate was recrystallised from petrol (60-80), m.p. 116-117°; N.M.R. (CDCl₃), 9.34 s broad [1] (C₁-H), 8.60 d [1] J=6.0 Hz (C₃-H), 8.4-7.4 complex [8] (Aromatic H plus C₄-H), 3.70 s [1] (COOCH₃); ν_{\max} , 1744, 1730, 1602, 1585; λ_{\max} (ϵ), 338 (3,600), 268 sh (6,500), 228 (54,500); mass m/e 307 (M⁺) [10%], 105 [100%]. (Found: C, 70.6; H, 4.3; N, 4.5; C₁₈H₁₃NO₄ requires: C, 70.4; H, 4.3; N, 4.6%).

7-Hydroxyisoquinoline-6-carboxylic acid (77)

The benzoyloxyisoquinoline (75) (620mg) was stirred with NaOH soln (30%, 20ml) for 24 hr. Acidification (HCl) gave a yellow solid which was collected and crystallised from 2NHCl, (200mg, 53%), m.p. 330°; N.M.R. (TFA) 11.67 s [1] and 11.1 s [1] (COOH and OH, removed by D₂O), 9.65 broad s [1] (C₁-H),

9.14 s [1], 8.07 s [1] and 8.54 broad s [2] (C_2-H , C_3-H , C_5-H and C_8-H); ν_{max} 3080-2100, 1420, 1302, 1050; λ_{max} 233, 277 sh, λ_{max} (EtOH/NaOH) 233, 277 sh; mass m/e 289 (M^+) [100%], 171 [100%], 143 [98%], 115 [90%], metastables at 120 and 92.4. (Found: C, 63.3; H, 3.8; N, 7.3. $C_{10}H_7NO_3$ requires C, 63.5; H, 3.7; N, 7.4%).

Attempts to protect the phenolic group of Methyl 7-hydroxy-isoquinoline-6-carboxylate (61) and methyl 1,2-dihydro-7-hydroxy-2-toluene-p-sulphonylisoquinoline-6-carboxylate (59)

METHOD	(61)	(59)
BENZYL ETHER FORMATION.		
NaH/DMF/Benzyl chloride RT. 3hr.	FAILED	FAILED
BENZYL ETHER FORMATION		
K_2CO_3 /MeOH reflux 12hr.	FAILED	FAILED
ACETATE FORMATION		
$(CH_3CO)_2O$ /pyridine 95° 4hr.	FAILED	
BENZOATE FORMATION		
2N NaOH/benzoyl chloride R.T. shake	FAILED	
BENZOATE FORMATION		
Benzoyl chloride/pyridine 95° 3hr.	FAILED	

Methyl 2-benzoyl-1-cyano-1,2-dihydro-7-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-6-carboxylate (75a)

A soln of methyl 2-benzoyl-7-benzyloxy-1-cyano-1,2-dihydroisoquinoline-6-carboxylate (4.0g) in dry DMF (40ml) was added to a stirred suspension of sodium hydride (0.4gm) in dry DMF (5ml) at 0° under N₂. When no more H₂ was evolved (10min), 3,4,5-trimethoxybenzylchloride⁶² (2.2g) in DMF (10ml) was added over 30min. Stirring was continued for 4hr, raising to room temp. after 90min. After excess sodium hydride had been decomposed by the addition of MeOH, the solvent was removed at 40° under reduced pressure to give a yellow solid which was recrystallised from MeOH as white plates (2.86g, 61%) m.p. 205°; N.M.R. (DMSO), 7.59 s [5] (N-COC₆H₅), 7.53 s [1] (C₅-H), 6.83 s [1] (C₈-H), 6.10 s [2] (C₆H₂(OMe)₃), 6.23 d [1] J=8.0 Hz (C₃-H), 5.72 d [1] J=8.0 Hz (C₄-H), 3.87 s [3] (-COOCH₃), 3.45-3.67 complex (-CH₂-Ar and 3 x Ar (OCH₃)); ν_{\max} , 3050, 1673, 1640, 1616, 1592, 1137; λ_{\max} (Σ), 305 (13,700), 238 (3,070); mass m/e 514 (M⁺) [1.0%], 105 [100%]. (Found: C, 67.5; H, 5.2; N, 5.4. C₂₉H₂₆N₂O₇ requires: C, 67.7; H, 5.1; N, 5.4%).

In an analogous experiment methyl 2-benzoyl-1-cyano-1,2-dihydro-5-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-6-carboxylate (76) was prepared (72%). Recrystallisation from MeOH afforded white plates, m.p. 202-203°; N.M.R. (DMSO), 7.70 d [1] J=8.7 Hz, 6.92 d [1] J=8.7 Hz (C₇-H and C₈-H), 7.59 s [5] (-N-COC₆H₅), 6.07 s [2] (-C₆H₂(OMe)₃), 6.41 d [1] J=8.0 Hz (C₄-H), 5.86 d [1] J=8.0 Hz (C₃-H), 3.94 s [3] (COOCH₃),

3.7-3.4 complex [11] ($-\text{CH}_2-\text{Ar}$ and $3 \times \text{Ar}(\text{OCH}_3)$); ν_{max} , 3060, 1675, 1640, 1598, 1135; λ_{max} (ξ), 367 (7,800), 260 (27,600), 239 (28,600); mass m/e 514 (M^+) [0.9%], 105 [100%]. (Found: C, 67.5; H, 5.1; N, 5.4. $\text{C}_{29}\text{H}_{26}\text{N}_2\text{O}_7$ requires: C, 67.7; H, 5.1; N, 5.4%).

Methyl 7-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-6-carboxylate (78).

The alkylated Reissert compound (75a) (1.8g) was stirred at room temperature for 30hr under N_2 in NaOMe soln. (2g Na in 150ml MeOH). Normal workup for phenolic bases left an insoluble yellow powder (80mg) which could not be crystallised, λ_{max} 380, 280 sh, 237; λ_{max} (EtOH/NaOH) 380, 285sh, 237; mass m/e 369 (M^+) [100%], 371 [47%]; (M^+ found: 369.1201; $\text{C}_{20}\text{H}_{19}\text{NO}_6$ requires 369.1212).

The NaOMe soln was therefore cautiously acidified with dry HCl gas and still under HCl gas, was heated under reflux for 3hr. The cooled solution was filtered, the solvent removed, and the residue basified with NaHCO_3 and extracted with CHCl_3 (3 x 50ml). The combined CHCl_3 extracts were washed (H_2O) dried (MgSO_4) and evaporated to give a pale yellow solid. Recrystallisation from MeOH afforded white crystals, m.p. $152-3^\circ$ (1.09g, 81%); N.M.R. (CDCl_3) 10.47 s [1] (OH , removed by D_2O), 8.40 s [1] (C_5-H), 7.63 s [1] (C_8-H), 8.38 d [1] $J=6.0 \text{ Hz}$ (C_3-H), 7.46 d [1] $J=6.0 \text{ Hz}$ (C_4-H), 6.52 s [2] ($-\text{C}_6\text{H}_2(\text{OCH}_3)_3$), 4.49 s [2] ($-\text{CH}_2-\text{Ar}$), 4.00 s [3] (COOCH_3), 3.77 s [9] ($\text{C}_6\text{H}_2-\text{OCH}_3$)₃; ν_{max} 3180 broad, 1683, 1632, 1598, 1132;

λ_{\max} (ϵ) 383 (3,800), 270sh (8,000), 243sh (53,000), λ_{\max} (ϵ) (EtOH/NaOH) 400, 296, (9,600), 253 (31,000), mass m/e 383 (M^+) [100%]. (Found: C, 65.9; H, 5.5; N, 3.8. $C_{21}H_{21}NO_6$ requires: C, 65.8; H, 5.5; N, 3.7%).

In an analogous experiment methyl 5-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-6-carboxylate (80) was prepared (90%) from (76) as pale yellow crystals from MeOH, m.p. 182-3°; N.M.R. ($CDCl_3$), 11.86 s [1] (\underline{OH} , removed by D_2O), 8.60 d [1] $J=6.0$ Hz ($C_3-\underline{H}$), 8.08 d [1] $J=6.0$ Hz ($C_4-\underline{H}$), 7.83 d [1] $J=8.8$ Hz ($C_7-\underline{H}$), 7.55 d [1] $J=8.8$ Hz ($C_8-\underline{H}$), 6.50 s [2] ($-C_6H_2(OCH_3)_3$), 4.56 s [2] ($-CH_2Ar$), 3.98 s [3] ($COOCH_3$), 3.76 s [9] ($-C_6H_2(OCH_3)_3$); ν_{\max} 320-3000, 1665, 1635, 1598, 1132; λ_{\max} (ϵ) 354 (4,800), 368 (4,800), 300sh (5,400), 290sh (6,300), 256 (22,900); mass m/e 383 (M^+) [100%]. (Found: C, 66.0; H, 5.6; N, 3.6. $C_{21}H_{21}NO_6$ requires: C, 65.8; H, 5.5; N, 3.7%).

Methyl 5-hydroxy-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (81)

Catalytic reduction of (71) (250mg) in EtOH (30ml) using Adam's catalyst at 60 lb/sq in. for 24 hr gave a pale yellow oil; N.M.R. ($CDCl_3$) 7.63 d [1] $J=8.0$ Hz ($C_7-\underline{H}$), 6.58 d [1] $J=8.0$ Hz ($C_8-\underline{H}$), 7.1 - 6.4 broad s [2] ($-OH$ and $-NH$, removed by D_2O), 4.1 - 3.85 complex [5] ($COOCH_3$ and $ArCH_2N$), 3.3-2.5 complex [4] ($C_3-\underline{H}_2$ and $C_4-\underline{H}_2$). The HCl salt was obtained as a white solid from MeOH (83%) m.p. 284-6° d. ν_{\max} 3500-3000, 2800-2200 (several bands), 1675, 1432, 1335, 1205, 1090; λ_{\max} (ϵ) 248 (8,650), 311 (3,400), mass m/e 207 (M^+-HCl) [46%], 178 [50%], 146 [100%] metastable at 119.8. (Found: C, 54.2; H, 5.6; N, 5.7; Cl, 15.0. $C_{11}H_{13}NO_3HCl$ requires C, 54.2; H, 5.7; N, 5.7; Cl, 14.5%).

Using the same method Methyl 1,2,3,4-tetrahydro-7-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-6-carboxylate (82) (540mg, 90%) prepared from (78) (600mg) in EtOH (150ml) as a pale yellow oil; N.M.R. (CDCl_3), 7.62 s [1] ($\text{C}_5\text{-H}$), 6.80 s [1] ($\text{C}_8\text{-H}$), 6.52 s [2] ($\text{C}_6\text{H}_2(\text{OMe})_3$), 4.49 t broad [1] $J=7$ Hz ($\text{C}_1\text{-H}$), 3.94 s [3] (COOCH_3), 3.82 s broad [9] ($3 \times \text{Ar-OCH}_3$), 3.6-2.6 complex [6] (aliphatics); ν_{max} (CHCl_3), 2800-2300, 3120, 1680, 1595, 1130. The hydrochloride was obtained as an off-white solid from benzene (575 mg, 80%) m.p. 186-188°; λ_{max} (ϵ), 320 (4,050), 243 (12,800). (Found: C, 59.2; H, 6.4; N, 3.1. $\text{C}_{21}\text{H}_{25}\text{NO}_6 \cdot \text{HCl}$ requires: C, 59.5; H, 6.2; N, 3.3%).

Similarly methyll,2,3,4-tetrahydro-5-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-6-carboxylate (83) was prepared from (80). The free base was obtained as an oil (88%). N.M.R. (CDCl_3), 7.64 d [1] $J=8.7$ Hz ($\text{C}_7\text{-H}$), 6.60 d [1] $J=8.7$ Hz ($\text{C}_8\text{-H}$), 6.5 s [2] ($\text{-C}_6\text{H}_2(\text{OMe})_3$), 4.55 t [1] ($J=7\text{Hz}$) ($\text{C}_1\text{-H}$), 3.93 s [3] (COOCH_3), 3.86-3.70 s broad [9] ($3 \times \text{Ar-OCH}_3$), 3.65-2.5 complex [6] (aliphatics); ν_{max} (oil film), 2800-2500 several bands, 1680, 1597, 1132. The hydrochloride was obtained as a white crystalline solid from benzene (80%) m.p. 213-215°; λ_{max} (ϵ), 312 (3900), 248 (12,700). (Found: C, 59.3; H, 6.3; N, 3.2; $\text{C}_{21}\text{H}_{25}\text{NO}_6 \cdot \text{HCl}$ requires: C, 59.5; H, 6.2; N, 3.3%).

1,2,3,4-Tetrahydro-7-hydroxy-6-hydroxymethyl-1-(3,4,5-trimethoxybenzyl)isoquinoline (14) LAH (0.15g) was added portionwise over 0.5hr to a soln of the hydrochloride of (700mg) in dry THF (30ml). The stirred mixture was heated under reflux for 2hr. and stirred at room temperature overnight.

The excess LAH was carefully destroyed with a few drops of water and the THF removed under reduced pressure at room temperature.

The residue was dissolved in 2N HCl, basified (NaHCO_3), and extracted CHCl_3 (5 x 20ml). The combined CHCl_3 extracts were washed with brine (3 x 20ml) dried (MgSO_4) and evaporated to yield a yellow oil, which on standing with benzene solidified.

Recrystallisation afforded a white crystalline solid (300mg, 51%), m.p. $129-130^\circ$; N.M.R. (CDCl_3), 6.63 s broad [2] (Aromatic H) 6.43 s [2] (Aromatic H), 5.5 s broad [3] (removed by D_2O), 4.65 s [2] ($\text{CH}_2\text{-OH}$), 3.78 s [9] (3 x Ar OCH_3), 4.4-3.6 complex [3] ($\text{-CH-CH}_2\text{-Ar}$) 3.3-2.4 complex [4] (Aliphatics); ν_{max} , 3280 sharp, 3500-3200, 1592, 1130; λ_{max} (ϵ), 285 (3000); mass m/e 355-359 cluster (M^+) [1%], 178 [100%]. (Found: C, 67.0; H, 6.9; N, 3.8. $\text{C}_{20}\text{H}_{25}\text{NO}_5$ requires: C, 66.8; H, 7.0; N, 3.9%.)

In an analogous experiment 1,2,3,4-tetrahydro-5-hydroxy-6-hydroxymethyl-1-(3,4,5-trimethoxybenzyl)isoquinoline (84) was obtained in 48% yield from the hydrochloride salt of (81). The white crystalline solid m.p. $175-177^\circ$ was obtained from benzene; N.M.R. (CDCl_3), 6.7 doublet of doublets [2] ($\text{C}_7\text{-H}$ and $\text{C}_8\text{-H}$), 6.47 s [2] (C_6H_2 (OMe)₃), 4.76 s [2] ($\text{-CH}_2\text{-OH}$), 3.82 s [9] (3 x Ar OCH_3), 4.5-3.7 complex [3] ($\text{-CH-CH}_2\text{-Ar}$), 3.4-2.4 complex [4] (4 x aliphatic H); ν_{max} , 3300 sharp, 3200-2600 broad 1598, 1140; λ_{max} (ϵ), 278 (2000); mass m/e 355-359 cluster (M^+) [1%], 178 [100%]. (Found: C, 66.8; H, 7.0; N, 3.9; $\text{C}_{20}\text{H}_{25}\text{NO}_5$ requires: C, 66.8; H, 7.0; N, 3.9%).

Isolation of the pavine (87) or isopavine (88) and the isoquinoline derivatives (85) and (86).

On one occasion the 1-benzylisoquinoline (78) formed in the normal manner from (75a) by treatment with NaOMe, followed by MeOH/HCl, was separated by P.L.C. on silica from three minor components. Elution with $C_6H_6/CHCl_3$, 50/50 afforded at Rf 0.7 a white crystalline solid (3%), m.p. 198-200° (MeOH) N.M.R. ($CDCl_3$) 8.6 s [1] and 7.78 s [1] (C_5-H and C_8-H), 8.52 d [1] $J=6$ Hz and 7.83 d [1] $J=6$ (C_3-H and C_4-H), 4.05 s [3] ($COOCH_3$), 10.78 s [1] (OH , removed by D_2O ; ν_{max} 3200 broad, 2220 (weak) 1698 (broad), 1495, 1295; λ_{max} 390, 280sh, 240; mass m/e 228 (M^+) [100%], 196 [100%]; (M^+ found: 228.0536; $C_{12}H_8N_2O_3$ requires 228.0535). This compound was considered to be methyl 1-cyano-7-hydroxyisoquinoline-6-carboxylate (85). At Rf 0.8 traces of a further component, tentatively assigned the ester structure (86), was isolated (1%) ν_{max} 3200 broad, 1743, 1690; λ_{max} 390, 285sh, 240; mass m/e 261 (M^+) [100%], 246 [60%].

From the slower running fractions of this chromatographic separation a white crystalline solid (X) (15%) was isolated m.p. 264° (MeOH). This was considered to be either the pavine (87) or the isopavine (88); N.M.R. ($CDCl_3$), 10.48 s [1] ($-OH$, removed by D_2O) 7.55 s [1] (aromatic H), 7.45 complex [5] ($N-COC_6H_5$), 7.0 s [1] (aromatic H), 6.3 s [1] (aromatic H) 5.40 d $J=1.6$ Hz and 5.31 d $J=1.6$ Hz [1] (methine H), 3.84 s [3] and 3.55 s [3] and 3.7 s [9] ($2 \times COOCH_3$ plus $-C_6H_2-(OCH_3)_3$), 4.3-2.7 complex [4] (aliphatic H); ν_{max} 3100 broad, 1745, 1685, 1655, 1625; λ_{max} (ϵ) 322(3,400), 245(12,600); mass m/e 547 (M^+) [37%], 486 [60%], 426 [90%], 105 [100%]. (Found: C, 65.90; H, 5.3; N, 2.4. $C_{30}H_{29}NO_9$ requires: C, 65.8; H, 5.3; N, 2.6%).

Attempted degradations of (X)

Compound (X) (275mg) was treated with NaOH soln (20ml) at steam bath temperature for 4hr. Acidification of the cooled soln with HCl and extraction into CHCl_3 afforded a white solid (194 mg, 73%) m.p. $281-4^\circ$ which was considered to be the acid derivative (95) or (96); part N.M.R. (CDCl_3) 7.6-7.4 broad [6], 6.95 s [1] 6.30 s [1] (2 x aromatic H), 5.35 broad s [1] (methine H), 3.68 s [9] ($\text{C}_6\text{H}_2(\text{OCH}_3)_3$) 3.51 s [3] (COOCH_3), ν_{max} 3500-2600, 1739, 1684, 1644; λ_{max} 312; λ_{max} (EtOH/NaOH) 313; mass m/e 533 (M^+) [90%], 474 [96%], 412 [100%]. (M^+ found: 533.1676; $\text{C}_{29}\text{H}_{27}\text{NO}_9$ requires 533.1686).

Compound (X) (140mg) was heated at 110° in polyphosphoric acid (4ml) for 2 hr. After this time a white solid (14mg) identified as benzoic acid by comparison of I.R. and M.S. with an authentic sample had sublimed from the reaction mixture. Examination of the residue afforded nothing identifiable. The acid (95) or (96) (45mg) was heated under reflux in EtOH (15ml) and Na metal (0.3g) for 20hr. Acidification of the cooled soln with HCl and extraction into CHCl_3 afforded starting acid (27mg).

Benzoylation of nor-amurensinine.

Nor-amurensinine⁶³ (30mg) in NaOH (10%, 3ml) was shaken for 20min with benzoyl chloride (0.2ml). The mixture was extracted into CHCl_3 (4 x 5ml) and the bulked extracts washed with 2N NaOH, 2N HCl and H_2O , dried (MgSO_4) and evaporated. Trituration of the residue with ether afforded an amorphous solid (30mg), ν_{max} 1628; mass m/e 429 (M^+) [11%], 308 [1%], 324 [4%], 295 [90%], 105 [100%], metastable at 203.

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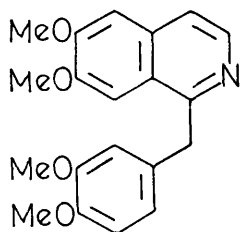
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CHAPTER 2

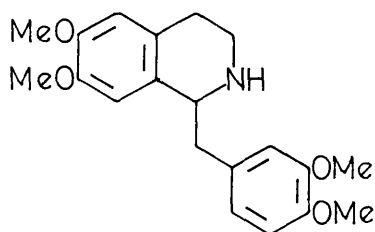
CHAPTER 2 : INTRODUCTION

1. Background to the isopavine ring system.

When papaverine (1) is reduced with tin and hydrochloric acid the major product is the expected tetrahydropapaverine (2), but a second base, called pavine¹, is formed in about 5% yield.

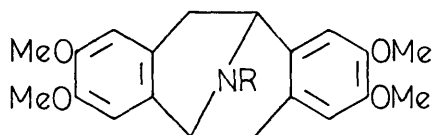


(1)

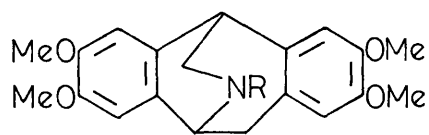


(2)

During the investigation on the structure of pavine, Schopf² proposed two possible structures for the base i.e. (3,R=H) and (4,R=H), and subsequently the former was shown to be correct by



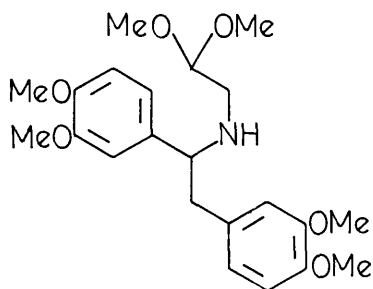
(3)



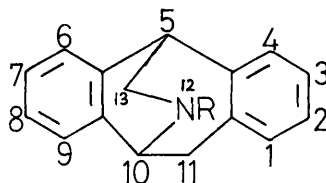
(4)

degradative studies. A satisfactory mechanism for the formation of (3) was proposed³. The isomeric base (4,R=H) was given the

trivial name isopavine by Battersby and Yeowell, who showed⁴ that this was the main product obtained from mineral acid treatment of the benzylaminoacetal (5). The isopavine ring system (6), 10,11-dihydro-10,5-iminomethano-5 H-dibenzo[a,d]-



(5)



(6)

cycloheptene is numbered as indicated.

2. Occurrence of isopavine alkaloids.

Alkaloids based upon the pavine ring system have been known for some time^{5,6} but an interesting recent development has been the isolation from plant sources and characterisation of the isopavine alkaloids. Table I summarises those naturally occurring compounds and for completeness includes those prepared in vitro.

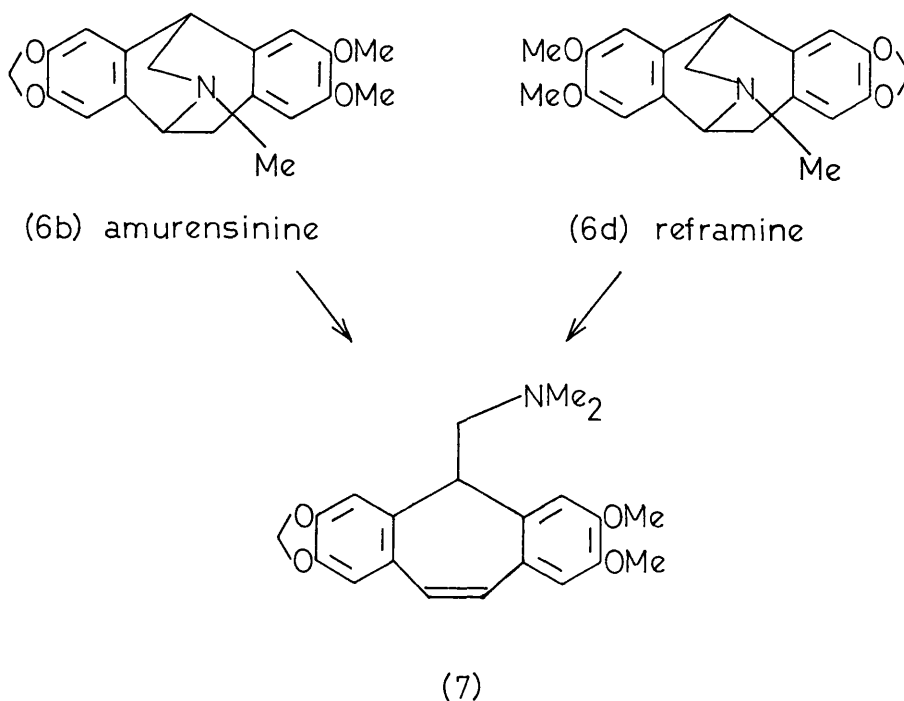
Table I

NAME	ORIGIN	SUBSTITUTION PATTERN						REFS
		2	3	7	8	12		
Amurensine 6a	Papaver alpinum " taticum	OH	OMe	0	CH ₂ O	Me		11,12,13
Amurensinine 6b	" pyrenaicum " silaveolens " nudicaule	OMe	OMe	0	CH ₂ O	Me		12,13
Reframidine 6c		0	CH ₂ O	0	CH ₂ O	Me		10
Reframine 6d	Roemeria refracta	0	CH ₂ O	OMe	OMe	Me		10
Remrefine 6e		0	CH ₂ O	OMe	OMe	(Me) ₂ ⁺		7,8,9
Thalisopavine 6f	Thalictrum dasycarpum	OH	OMe	OMe	OMe	Me		14
Reframoline 6g 6h	Roemeria refracta	0	CH ₂ O	OH	OMe	Me		
		0	CH ₂ O	OMe	OH	Me		10
Isopavine* 6i		OMe	OMe	OMe	OMe	H		4
O-methyl thalisopavine* 6j		OMe	OMe	OMe	OMe	Me		14
iscamurensine* 6k		OMe	OH	0	CH ₂ O	Me		15

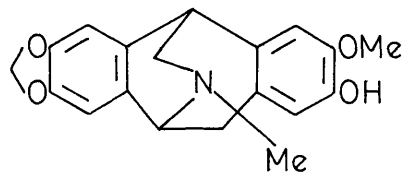
* not isolated from plant material

3. Elucidation of structure of isopavine alkaloids

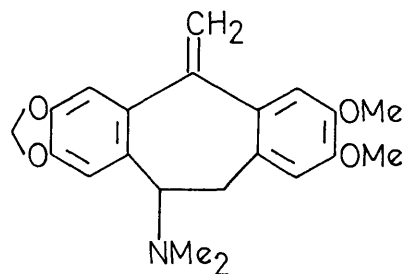
The structures of the isopavine alkaloids have been deduced, in the main, by Hofmann degradation procedures and by interpretation of mass spectral fragmentation patterns. Although the former method is satisfactory for the determination of the basic skeleton present, it can be, as shown below, ambiguous for the placing of substituents.



The structures of amurensine (6a) and amurensinine (6b) were elucidated by Santavy et al¹² who showed that the methine base (8) of amurensinine was formed in small yield along with the normal degradation product (7). Exhaustive Hofmann methylation procedures carried out on (7) and (8) afforded the

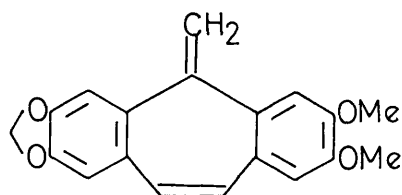


(6a) amurensine



(8)

expected bismethine (9), which showed very similar spectral characteristics to those bis-methines prepared from synthesised

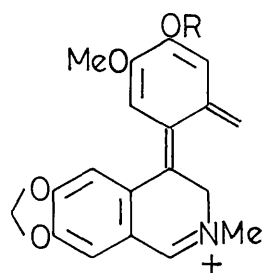
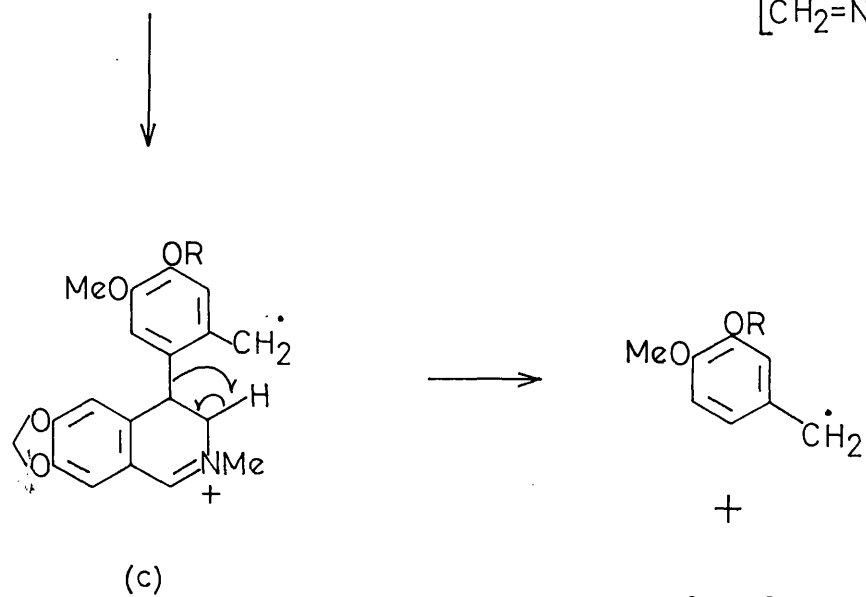
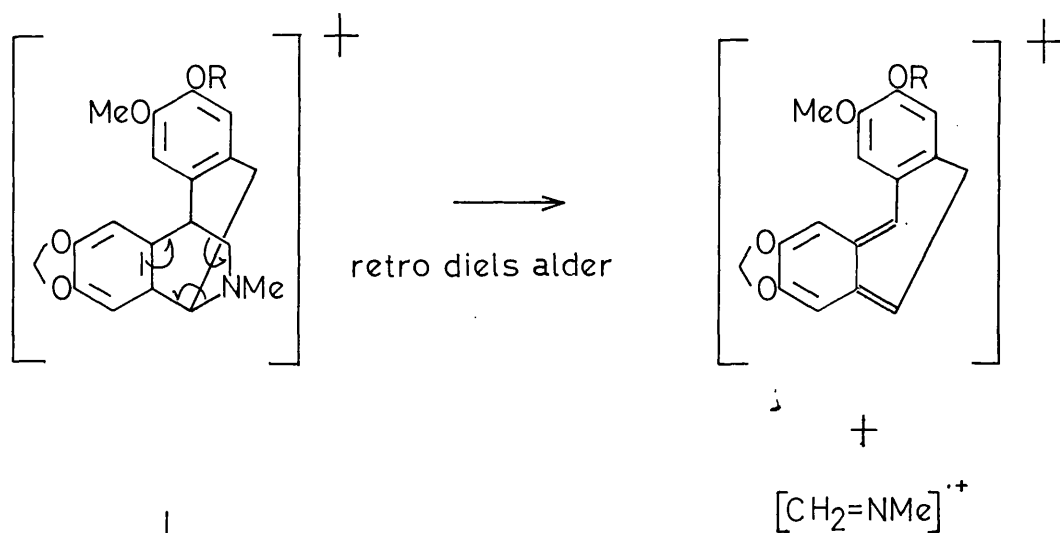


(9)

isopavines. The methylenedioxy function was placed as a result of potassium permanganate degradation studies. The free hydroxy group of amurensine (6a) was not placed with any certainty by Santavy et al, but was shown later, by synthesis¹⁵, to be at position C₂.

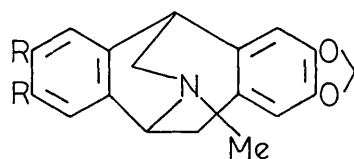
Dolejs and Hanus¹⁶ confirmed these assignments in a study of the mass spectra of both alkaloids. The fragmentation pattern, discussed in Chapter I of this thesis, p.60-1, is summarised in

Scheme I



Scheme I, which explains the formation of the base peak ion "a" from isomerisation of the ionised molecule to the imminium ion "c" with the simultaneous opening of the benzylic bridge. The fragmentation pattern of isopavine alkaloids is simple but specific enough for the identification of this group from other types of alkaloids including the closely related pavines¹⁷.

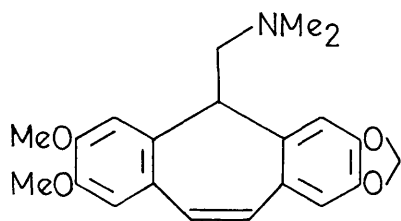
Slavik et al¹⁰ reported the isolation and characterisation of of the two laevoratory isopavine alkaloids, reframine (6d) and reframidine (6c)¹⁸. The first Hofmann degradation product (10)



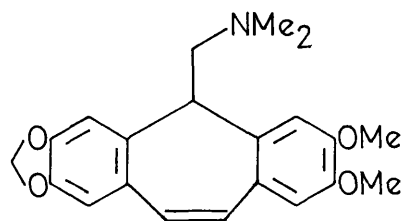
(6d) R=OMe reframine

(6c) RR=OCH₂O reframidine

of reframine, although chemically identical with 2-methyl-amurensinine methine (7) showed a mirror image optical rotatory dispersion (O.R.D.) curve in agreement with the reversed position



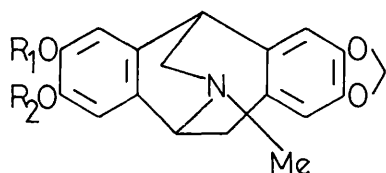
(10)



(7)

of the substituents in the aromatic nucleii of the natural products.

In the same study¹⁰ a phenolic isopavine alkaloid called reframoline was isolated. Its I.R. and U.V. spectra were very similar to those of reframine (6d), and monomethylation of reframoline gave a base identical with reframine. The possible structures (6g) and (6h) considered for the alkaloid were supported



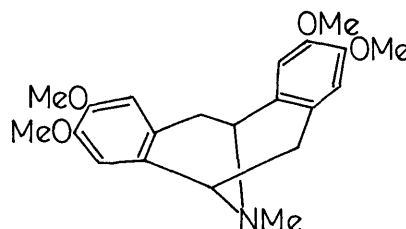
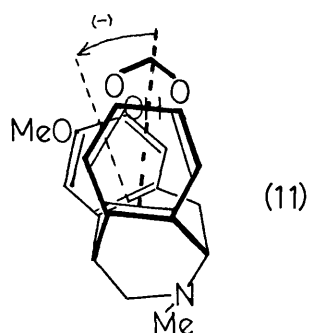
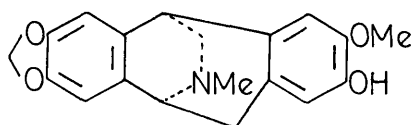
(6g) $R_1 = \text{Me}$, $R_2 = \text{H}$

(6h) $R_1 = \text{H}$, $R_2 = \text{Me}$

by its mass spectral characteristics, but the position of the phenolic hydroxy group was not determined. The object of the work described in this chapter is to settle this uncertainty.

4. Stereochemistry and Biosynthesis of pavine and isopavine alkaloids

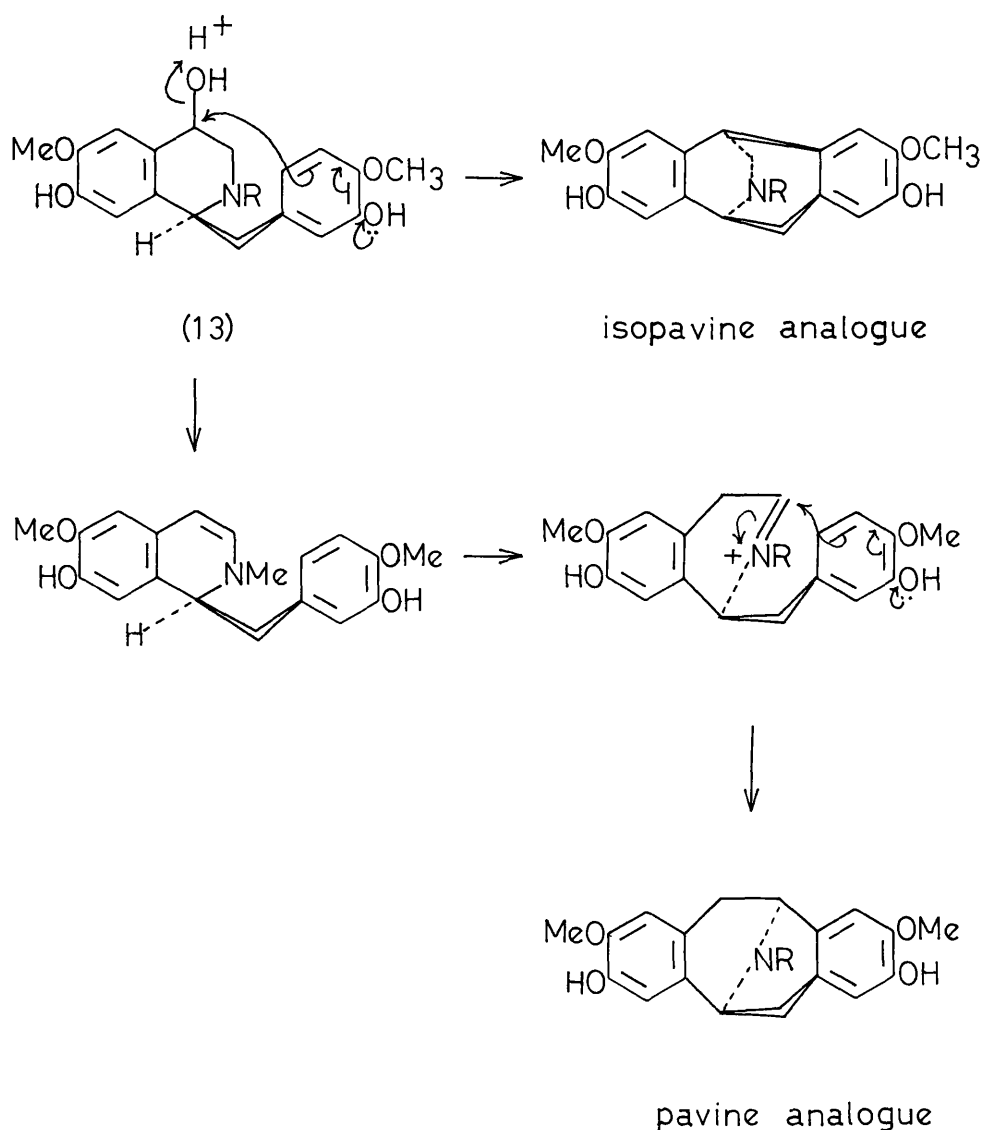
The absolute configuration of the isopavine alkaloid (-) amurensine is depicted in (11), and was deduced¹⁹ by circular dichroism (c.d) studies analogous to those employed in the study of the pavine alkaloid (-) argemonine (12)^{20,21}, which has also



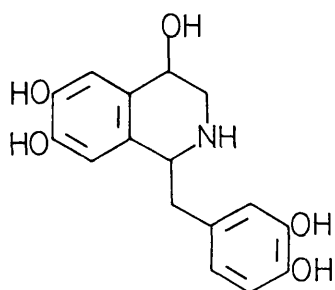
(12)

been studied by degradative methods¹². In both pavine and isopavine alkaloids the nitrogen bridge is situated below the V plane of the molecules, and Shamma and Moniot^{19,27} suggest the possibility of a common biogenetic precursor such as 4-hydroxyreticuline (13), which depending on the plant family or genus, is cyclised directly to an isopavine species or alternatively undergoes dehydration, double bond isomerisation and intramolecular cyclisation to the pavine analogue as shown in Scheme 2.

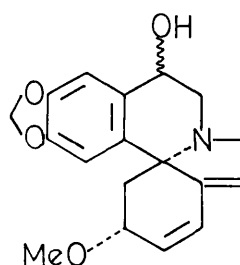
Scheme 2.



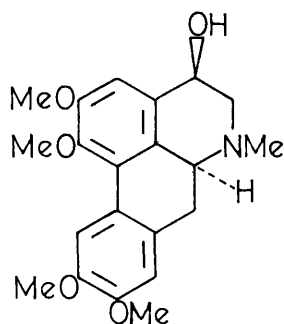
Earlier, Dyke et al^{27,23} had speculated that 4-hydroxy-norlaudanosoline (14) may be the formal precursor of a diverse group of alkaloids parallelling those derivable from norlaudanosoline itself⁵. Support for such postulates is provided by the isolation



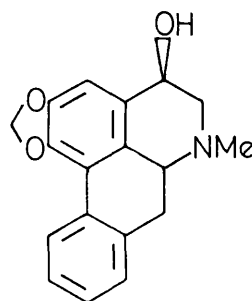
norlaudanosoline (14)



erythrine (15)



cataline (16)



steporphine (17)

from plant sources of such alkaloids as (15)²⁴, (16)²⁶ and (17)²⁵.

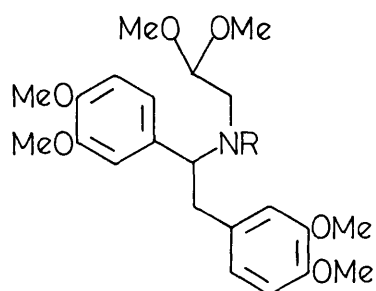
As the aporphine group of alkaloids are considered to be biosynthesised from 1-benzylisoquinolines through phenolic coupling⁵, such intermediacy of 4-hydroxy-norlaudanosoline (14) is possible. Table 2 shows some of the other groups of isoquinoline alkaloids which have been isolated within the genera producing pavines and isopavines.

TABLE 2

	Isopavine	pavine	proaporphine	aporphine	berberine	protopine	benzo [c] phenanthridine
argemone	-	+	-	-	+	+	+
cryptocarya	-	+	-	+	-	-	-
eschsoltzia	-	+	-	-	-	+	+
papaver	+	-	+	+	+	+	+
roemeria	+	-	+	+	+	+	-
thalictrum	+	+	-	+	+	-	-

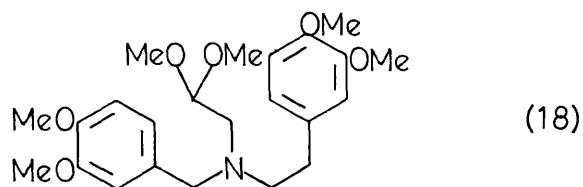
5. Synthesis of isopavine alkaloids.

Several synthetic methods have been used to confirm the structures of the alkaloids discussed and the first involves the treatment of the aminoacetal (5) with mineral acid⁴. By analogy with the double cyclisation of the aminoacetal (18) to (20), which

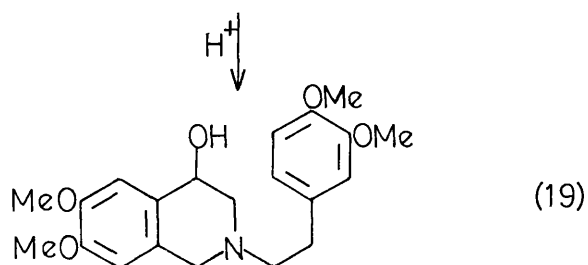


(5)

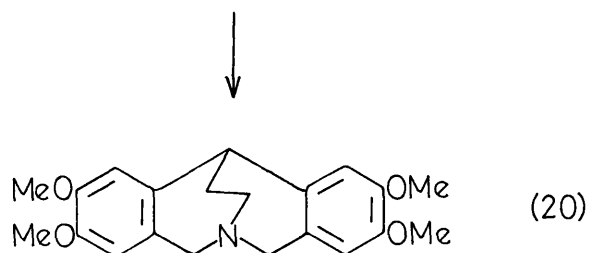
was shown to involve the 4-hydroxy-tetrahydroisoquinoline (19)²⁷,



(18)

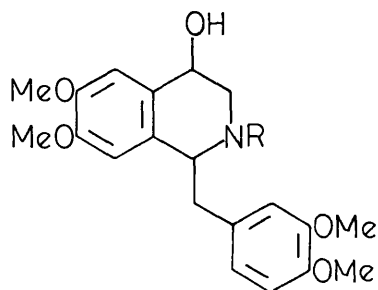


(19)



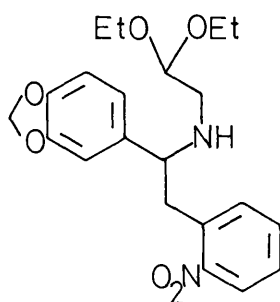
(20)

it was postulated²⁸ that the cyclisation of (5) also involves prior formation of a 4-hydroxy-tetrahydroisoquinoline intermediate (21)

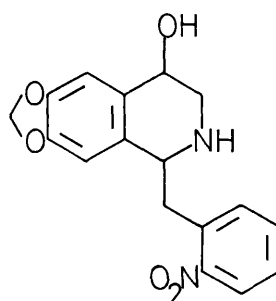


(21)

Although there is circumstantial evidence for such intermediacy²⁹ the only authenticated example³⁰ is (23) formed by acid treatment of the acetal (22). The electron deficiency of the nitrophenyl



(22)



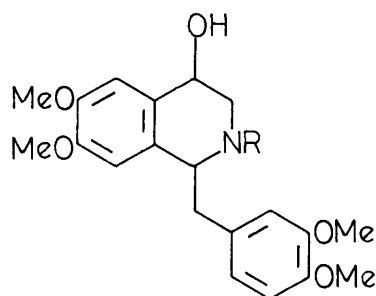
(23)

ring presumably prevents nucleophilic displacement of the 4-hydroxy group to give the isopavine system.

Subsequently amurensinine (6b) was synthesised²⁷ by the route summarised in Scheme 3 in which the Schiff's base (24) was prepared by condensation of aminoacetaldehyde dimethyl acetal with the deoxybenzoin (25a). Subsequent reduction and cyclisation afforded the NH isopavine (26) which was N-methylated by treatment with formaldehyde followed by sodium borohydride.

From the appropriate ketones (25), thalisopavine (6f)¹⁴, reframine (6d) and reframidine (6c) were similarly prepared.

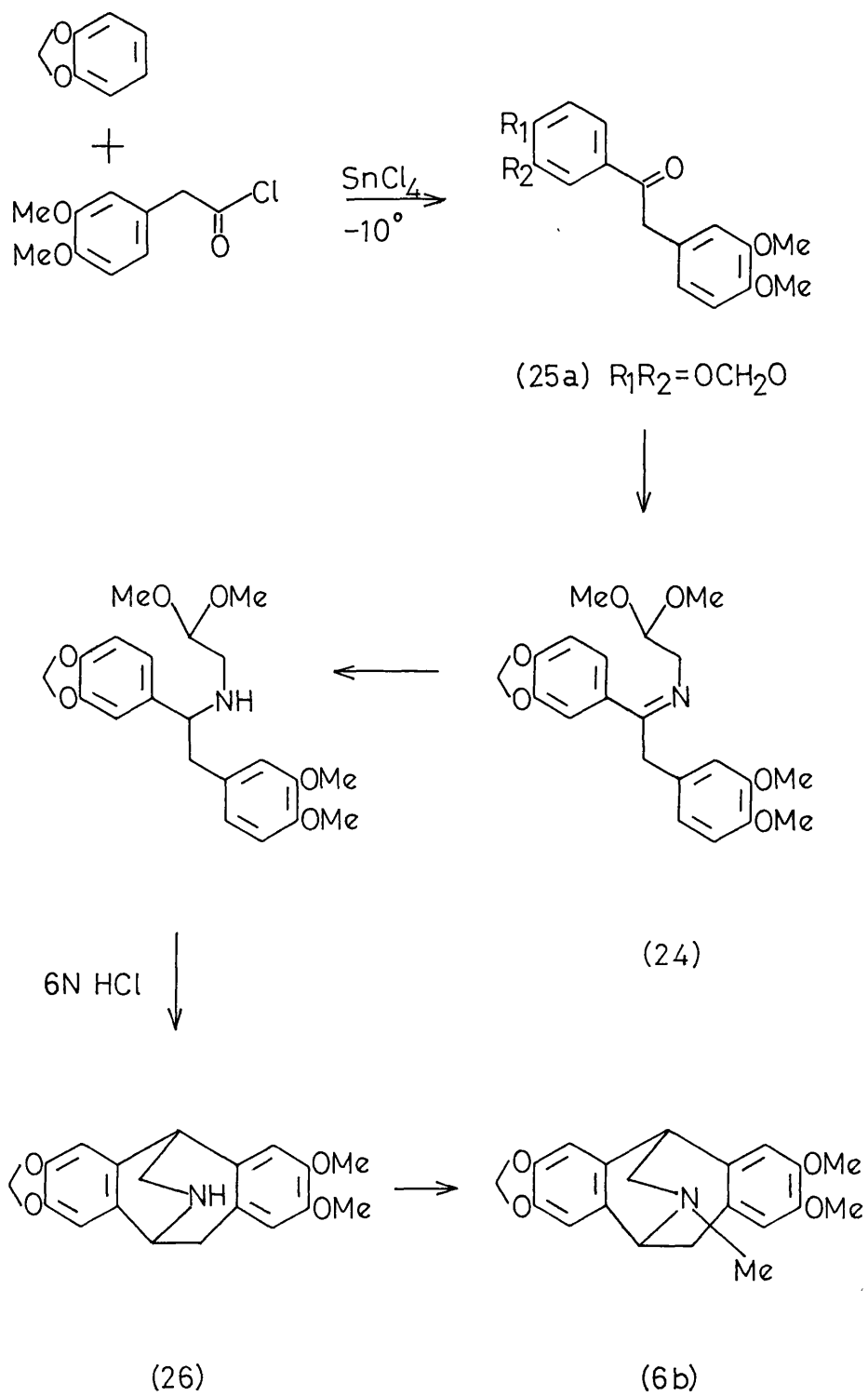
Dyke and Ellis²³, in an alternative approach, generated 2-methyl-4-hydroxy-1,2,3,4-tetrahydropapaverine (21, R=Me),



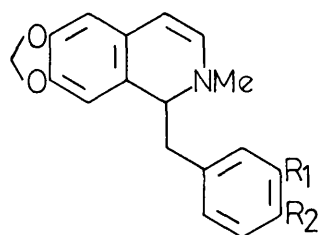
(21, R=Me)

by treatment of 2-methyl-1,2,-dihydropapaverine with diborane followed by hydrogen peroxide. Cyclisation of (21, R=Me) using mineral acid afforded o-methylthalisopavine (6j). In a subsequent paper¹⁵ the same authors reported an analogous synthesis of amurensine (6a) and isoamurensine (6k) from the corresponding

Scheme 3



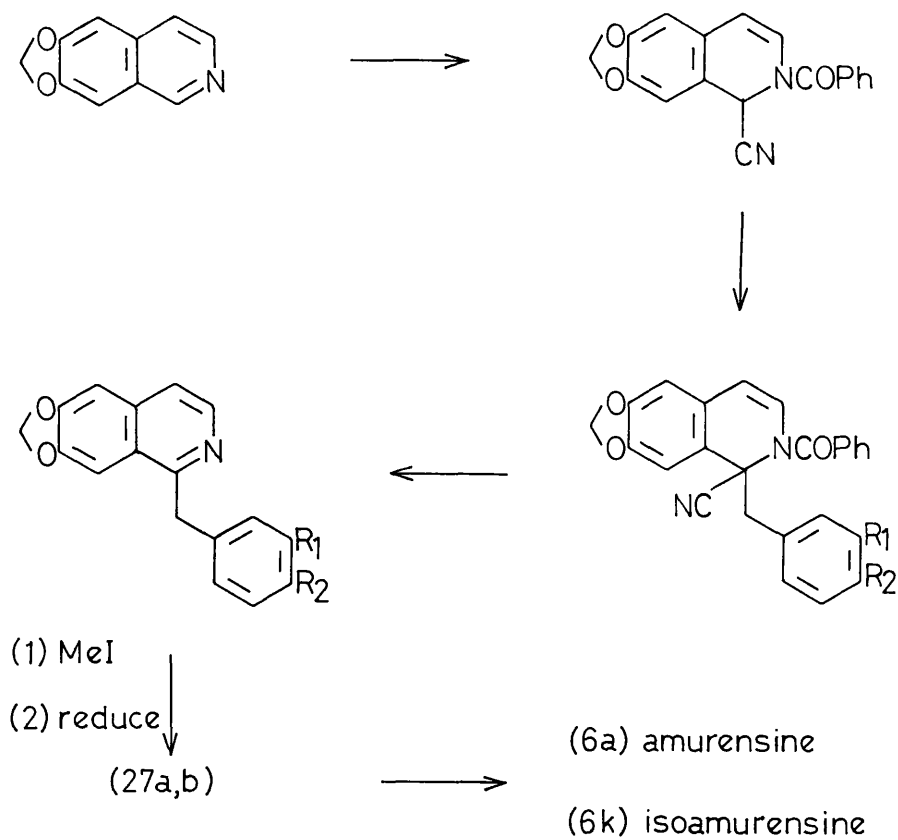
1-benzyl-1,2-dihydroisoquinolines (27a) and (27b), which were prepared via the Reissert reaction as outlined in Scheme 4.



(27a) $R_1 = \text{OCH}_2\text{Ph}$, $R_2 = \text{OMe}$

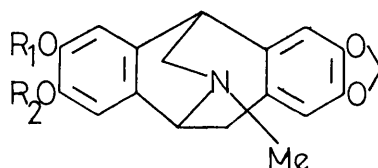
(27b) $R_1 = \text{OMe}$, $R_2 = \text{OCH}_2\text{Ph}$

Scheme 4.



6. OBJECTIVES

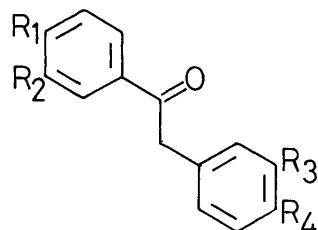
The subject of the work described in this chapter is the preparation of the two possible isomeric structures of reframoline (6g) and (6h) for comparisons with an authentic sample of the alkaloid. It was planned to use the phenolic deoxybenzoins



(6g) $R_1=H, R_2=Me$

(6h) $R_1=Me, R_2=H$

(25b) and (25c) in an analogous manner to that described in Scheme 3 (p.110). Numerous attempts³¹ to synthesise these



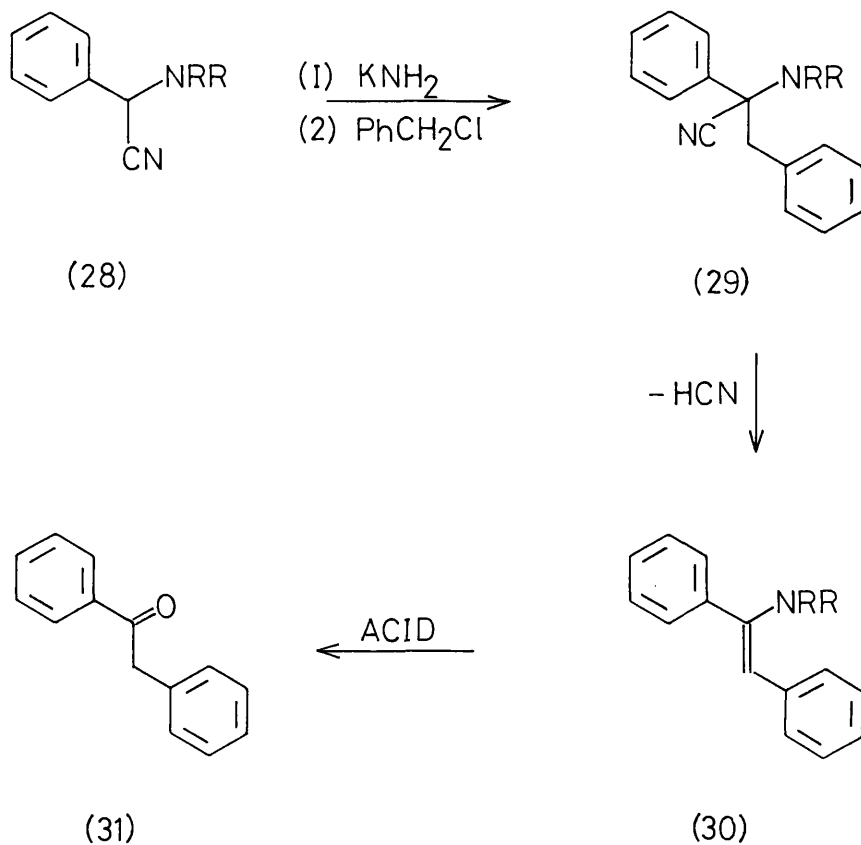
(25b) $R_1=OH, R_2=OMe, R_3R_4=OCH_2O$

(25c) $R_1=OMe, R_2=OH, R_3R_4=OCH_2O$

deoxybenzoins, however, have resulted in failure, and as the general methods available^{32,a,b,c,d,e} seem unsuitable a more versatile method was sought.

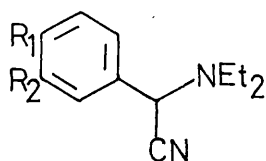
DISCUSSION1. Deoxybenzoin synthesis.

A versatile deoxybenzoin synthesis was reported by Hauser et al^{33a,b} in which the aminonitrile (28) is alkylated with a benzyl halide in the presence of potassium amide in liquid ammonia. Dehydrocyanation of the product (29) forms the enamine (30), acid hydrolysis of which gives the deoxybenzoin (31). This method, however, has received little attention which



is surprising in view of the availability of aminonitriles^{34a,b,c,d}, and the possible synthetic utility of deoxybenzoins^{35a,b,c} especially in alkaloid synthesis^{30,36a,b,c}. The two methods most commonly used for the preparation of aminonitriles are (a)

treatment of an amine hydrochloride and sodium cyanide with an aldehyde in aqueous alcohol^{34a}, or (b) reaction of an amine and sodium cyanide with the bisulphite addition complex of an aldehyde^{34b}. Method (a) was found in the author's experience to be the more successful for the preparation of the aminonitriles (32a-c) whereas neither method gave the phenolic compound (32d).



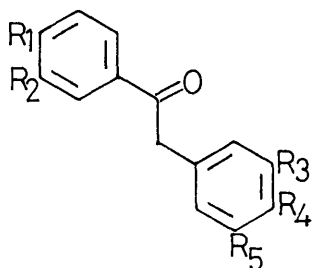
(32a) $R_1 = \text{OCH}_2\text{Ph}$, $R_2 = \text{OMe}$

(32b) $R_1 = \text{OMe}$, $R_2 = \text{OCH}_2\text{Ph}$

(32c) $R_1 = R_2 = \text{OMe}$

(32d) $R_1 = \text{OH}$, $R_2 = \text{OMe}$

Alkylation of (32c) with benzyl chloride in the presence of potassium amide in liquid ammonia, followed by dehydrocyanation and acid treatment of the enamine afforded a disappointing yield (35%) of the deoxybenzoin (33a). Attempts to improve this yield



(33a) $R_1 = R_2 = \text{OMe}$, $R_3 = R_4 = R_5 = \text{H}$

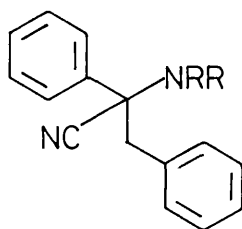
(33b) $R_1 = \text{OCH}_2\text{Ph}$, $R_2 = \text{OMe}$, $R_5 = \text{H}$, $R_3R_4 = \text{OCH}_2\text{O}$

(33c) $R_1 = \text{OMe}$, $R_2 = \text{OCH}_2\text{Ph}$, $R_5 = \text{H}$, $R_3R_4 = \text{OCH}_2\text{O}$

(33d) $R_2 = \text{OCH}_2\text{Ph}$, $R_1 = R_3 = R_4 = R_5 = \text{OMe}$

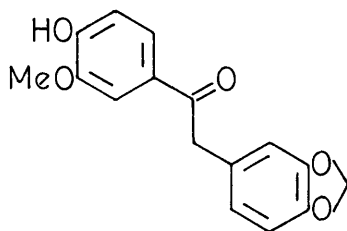
(33e) $R_1 = R_2 = R_3 = R_4 = \text{OMe}$, $R_5 = \text{H}$

utilizing sodium diisopropylamide, instead of potassium amide in liquid ammonia failed, but sodium hydride in dimethylformamide (D.M.F.) facilitated alkylation and the deoxybenzoins (33a-e) were prepared in good yield using this modification. A range of deoxybenzoins were subsequently synthesised in these laboratories³⁷, to demonstrate the versatility of this reaction, and intermediates of the type (34) have been isolated. The preparative value



(34)

of this technique for unsymmetrically substituted phenolic deoxybenzoins was demonstrated by the hydrogenolysis of (33b) to give a high yield of (25b). It was found that if the reaction

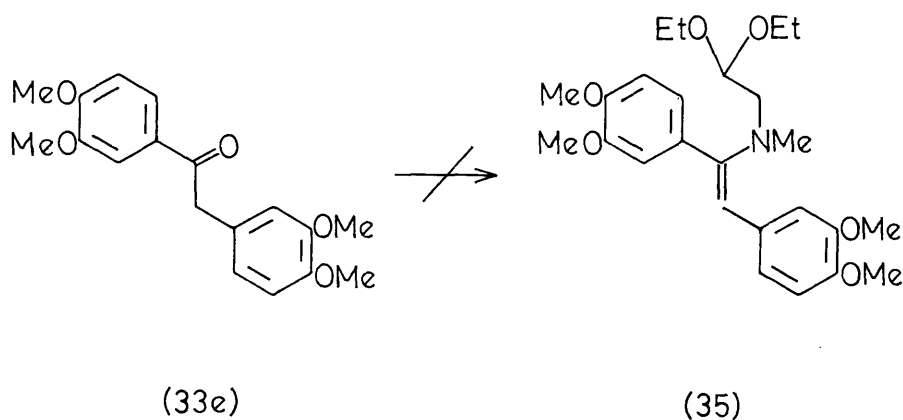


(25b)

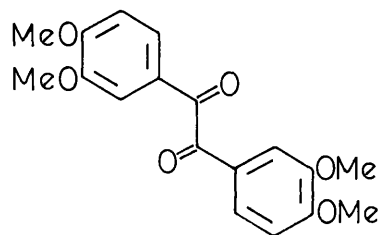
was stopped after the uptake of only one equivalent of hydrogen the carbonyl function was not affected.

Imine formation

The first attempt to construct the required benzylbenzylamine system involved the condensation of N-methylaminoacetaldehyde-diethylacetal with the model ketone (33e). Only starting material, however, could be recovered using a variety of conditions based on



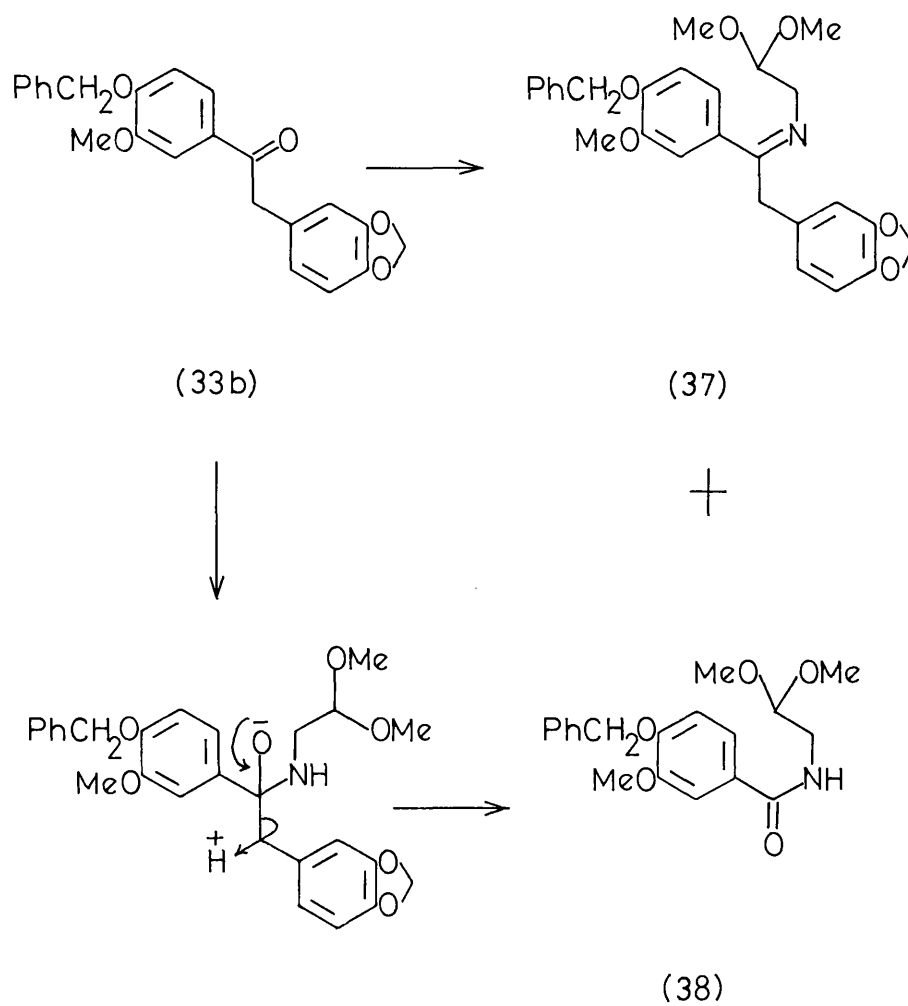
the azeotropic distillation method. When the reaction was conducted in methanol in the presence of caustic soda, in addition to unchanged ketone, a product was isolated which exhibited a carbonyl absorption frequency in its I.R. spectrum at 1650cm^{-1} , 20cm^{-1} lower than the deoxybenzoin. This compound showed no absorption in its N.M.R. spectrum due to a benzylic methylene group and from its mass spectrum was shown to possess a molecular weight of 330 consistent with the veratril structure (36). The base peak of the spectrum was predictably at 165m/e , and the melting point corresponds with the literature value⁴.



(36)

The I.R. carbonyl stretching frequency of 1670cm^{-1} exhibited by deoxybenzoins indicates a diminished reactivity towards nucleophiles compared with benzaldehyde (1700cm^{-1}). The condensation to give (35) requires the formation of a $\text{C}=\text{N}^+$ or a $\text{C}=\text{C}$ which is energetically less favourable than formation of the imine (37) which was shown to form reasonably readily. Reaction of the ketone (33b) with aminoacetal required heating under reflux in toluene with a trace of p-toluenesulphonic acid. A minor product of this reaction analysed for $\text{C}_{18}\text{H}_{21}\text{NO}_5$ and exhibited absorptions in its I.R. spectrum at 1630 and 3280cm^{-1} . Its N.M.R. spectrum (p162) showed that there was no methylenedioxy function, but that the aromatic methoxy, the benzyl ether and acetal groupings were present. The compound was assigned structure (38) which also explained the slightly extended benzenoid red-shift conjugation shown in its U.V. spectrum. No precedent for this type of reaction could be traced but Scheme 5 is tentatively suggested to explain its formation, although no 3,4-methylenedioxy toluene was found.

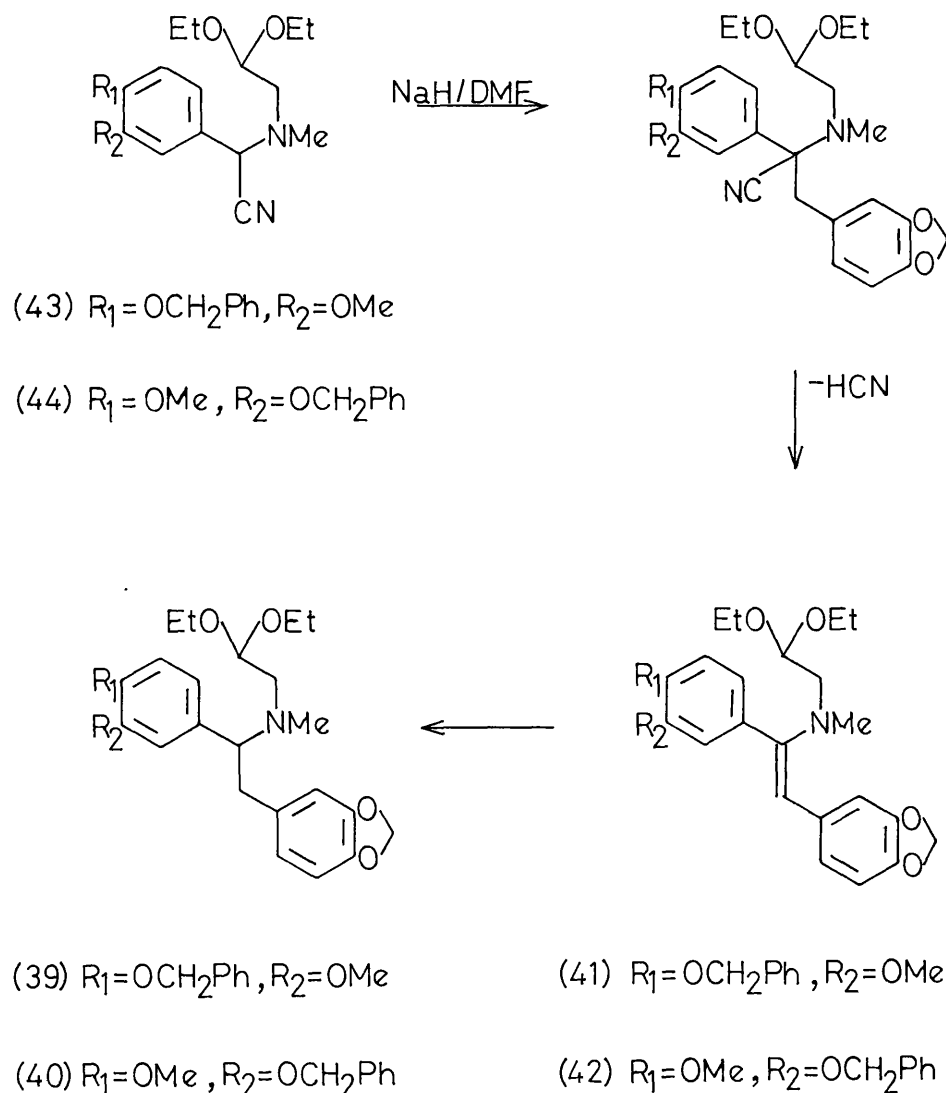
Scheme 5



The reaction was repeated using the tetramethoxy ketone (33e), but none of the corresponding amide was detected. In addition to the expected Schiff's base only veratril (36) was isolated, a known side reaction under these conditions⁴.

2. Aminonitrile route to isopavines and pavines.

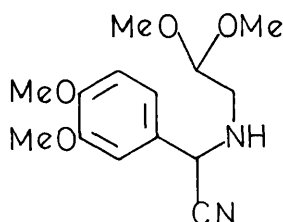
In order to synthesise the desired isomeric isopavines (6g) and (6h) a more interesting and novel extension of the aminonitrile route was investigated, in preference to the elaboration of the deoxybenzoins. It was the intention to prepare the required benzylbenzylamines (39) and (40) by reduction of the enamines (41) and (42) formed by alkylation and dehydrocyanation of the novel aminonitriles (43) and (44).



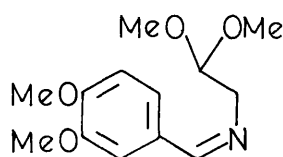
Aminonitrile formation

Although the sodium bisulphite method failed to give a good yield of the required aminonitrile (43) the alternative procedure which involves treatment of the aldehyde with N-methylacetaldehydediethyl acetal hydrochloride and sodium cyanide afforded a viscous pale yellow liquid, the I.R. spectrum of which showed an absorption at 2215cm^{-1} attributable to the nitrile group. The N.M.R. spectrum contained a singlet absorption at 5.01δ corresponding to the methine proton alpha with respect to the nitrile group. A high resolution mass measurement of the molecular ion confirmed the molecular formula of $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4$ and the structure (43).

An analogous reaction with aminoacetaldehydedimethyl acetal hydrochloride and veratraldehyde gave (45) which on treatment



(45)

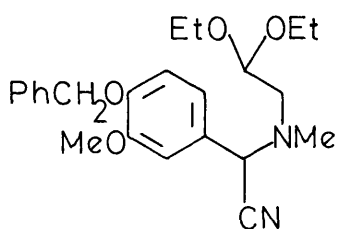


(46)

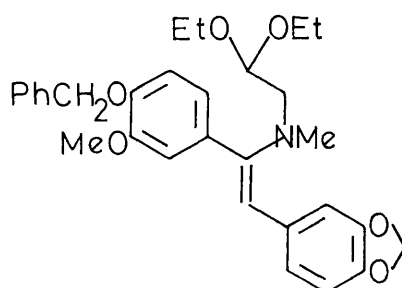
with base afforded the known schiffs base (46).

The Alkylation reaction

Alkylation of (43) with 3,4-methylenedioxybenzyl chloride in the presence of sodium hydride in D.M.F., with subsequent elimination of HCN in vacuo afforded an oil which was shown by its I.R. spectrum to possess no nitrile group. The mass spectrum of this material exhibited a peak at m/e 505 which persisted at low electron voltage. Attempts to purify by distillation were unsuccessful,⁵⁰ so what was assumed to be the crude enamine (41) was treated with sodium borohydride in hot



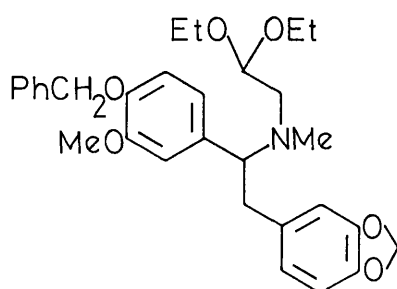
(43)



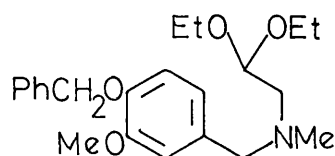
(41)

aqueous ethanol and the basic product extracted from ether into ice-cold dilute acid. Examination of this by T.L.C. showed the presence of one major and one minor product, which were separated by P.L.C. The N.M.R. spectrum of the major product showed an N-methyl absorption at δ 2.35 and the presence of a methylenedioxy function at δ 5.92 and two equivalent ethoxy

groups. A low intensity molecular ion at 507 m/e was evident in the mass spectrum and peaks corresponding to the fragmentation and loss of the acetal function, were prominent. A facile loss of the methylenedioxy benzyl function (m/e 135) from the molecular ion was also evident which is consistent with the required structure (39b). The minor component, whose N.M.R. spectrum



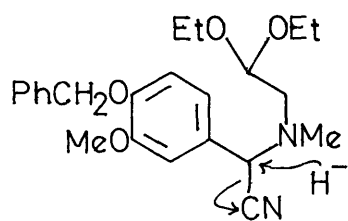
(39b)



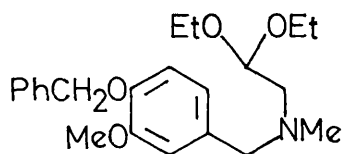
(47)

differed mainly from that of (39b) by the absence of peaks due to the methylenedioxy benzyl group, and the presence of a two proton singlet at δ 3.15, was assigned the structure (47). It is probable that this resulted from a hydride ion displacement of the nitrile group in some unalkylated aminonitrile (43) (route A), or by reduction of the imminium salt (48) (route B).

Although much less likely there is a further possible route by which (47) could be formed which is considered in the light of a report³⁸ that cleavage occurs in the reduction of

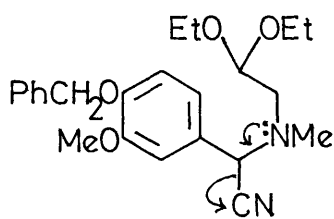


(43)

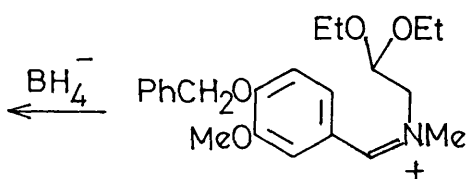


(47)

Route A



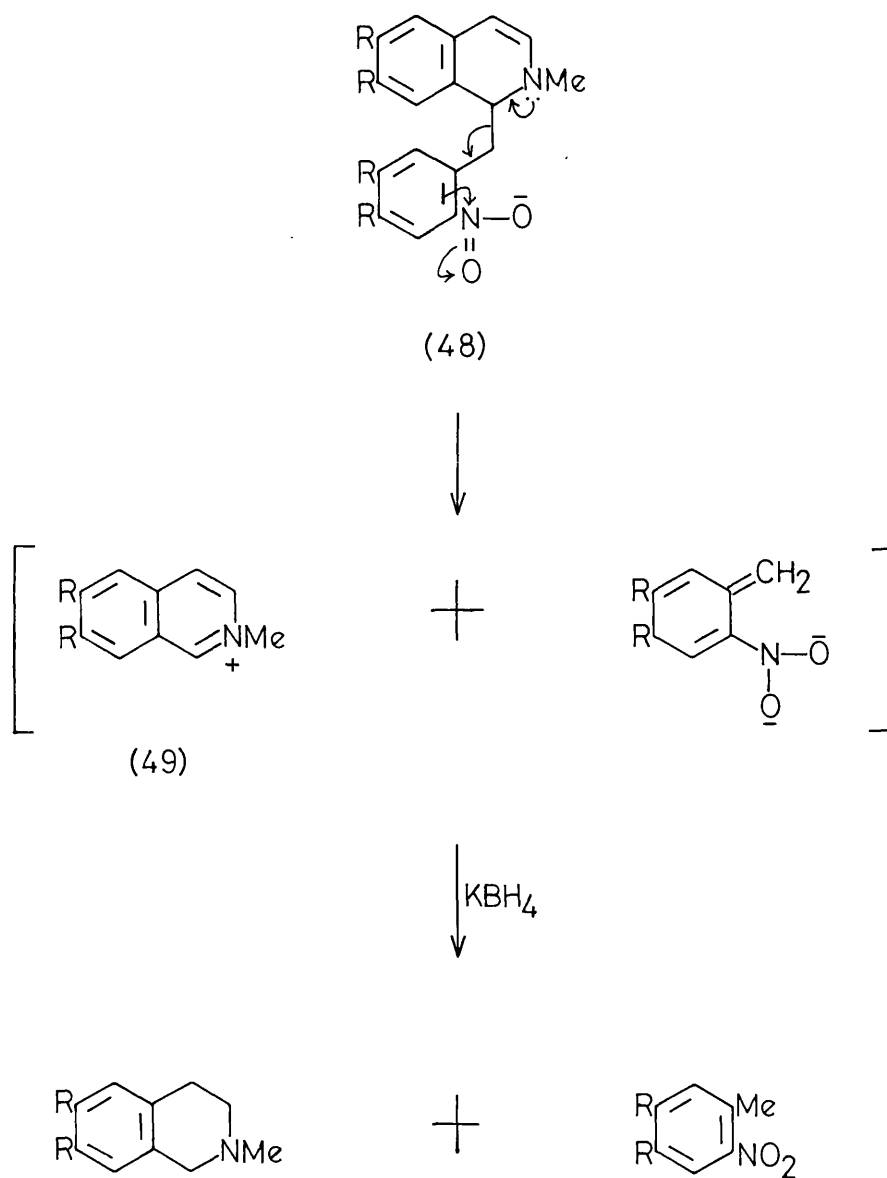
(43)



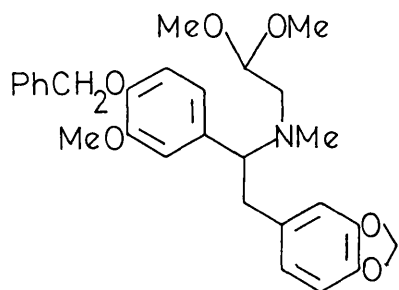
Route B

1-benzyl-1,2-dihydroisoquinolines of the type (48) with potassium borohydride, to give the 1,2,3,4-tetrahydroisoquinoline and a toluene derivative. The postulated mechanism (Scheme 6) suggests the intermediacy of an isoquinolinium salt (49), this author suggests that it is more likely that the enamine (48) would be reduced to its tetrahydro-derivative prior to any cleavage.

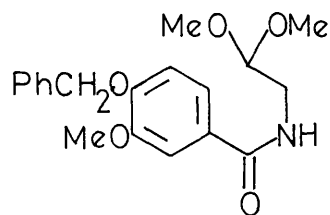
Scheme 6



However, the loss of a C_1 substituent would rely on its ability to stabilise a negative charge. The nitro group in (48) presumably facilitates the cleavage whereas the methylene dioxybenzyl group in (39b) is less likely to promote a similar reaction. It is interesting to note that a similar pathway



(39b)

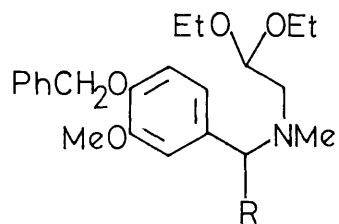


(38)

was suggested on page 118 to explain the formation of the amide (38).

Cyclisation of (39) with hydrochloric acid.

Thus far in the desired isopavine synthesis the novel aminonitrile (43), prepared directly from vanillin o-benzyl ether is converted directly to the alkylated acetal (39) contaminated with up to 10% of (47).



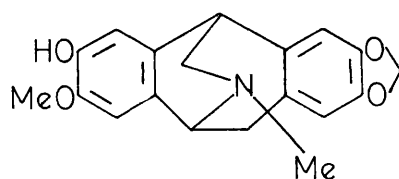
(43) R = CN

(39) R = 3,4-methylenedioxybenzyl

(47) R = H

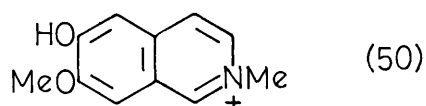
Experimentally it was found satisfactory to carry out the double cyclisation on the impure acetal (39) and to purify the products by P.L.C. By this means treatment of the mixture with six normal hydrochloric acid at room temperature for sixteen hours followed by four hours at steam bath temperature gave a good yield of phenolic bases.

Chromatographic separation of the reaction product on alumina afforded a white crystalline solid, the N.M.R. spectrum of which showed the presence of four aromatic protons, confirming that double cyclisation had occurred. The mass spectrum showed a molecular ion at 325 m/e, a peak at $M^+ - 1$, and a prominent peak at $(M^+ - 43)$ which is in accord with the expected "bridge loss" observed with the isopavine skeleton. The isopavine structure (6g) was supported



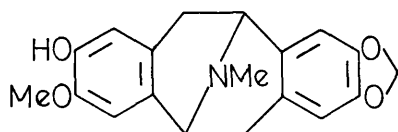
(6g)

by the presence of a base peak in the mass spectrum corresponding to the isoquinolyl cation (50), (see p 154).

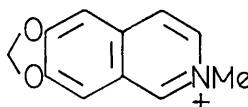


(50)

Chromatographic separation of the residues on silica afforded a second phenolic base, as a crystalline solid from acetone. Its N.M.R. spectrum exhibited absorptions due to four aromatic protons, and microanalytical data confirmed an empirical formula of $C_{19}H_{19}NO_4$. The mass spectrum confirmed the pavine structure (51) by the presence of base peaks corresponding to the isoquinolyl cations (50) and (52). No peak corresponding to M^+-43 was evident, (see p 152).



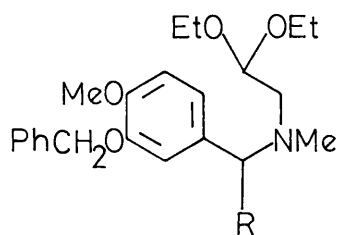
(51)



(52)

Preparation and cyclisation of (40)

In order to prepare the isomeric isopavine structure (6h) an exactly analogous route was followed which involved the formation of the aminonitrile (44) and its elaboration by alkylation, dehydrocyanation, and its reduction to the benzylbenzylamine (40) (for N.M.R. spectra see p 151). Small amounts of the unalkylated material (53) were formed, and although a sample of the mixture was separated by P.L.C. for structural confirmation, it was preferred to cyclise the

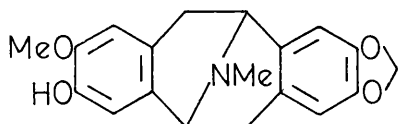


(40) R=3,4-methylenedioxybenzyl

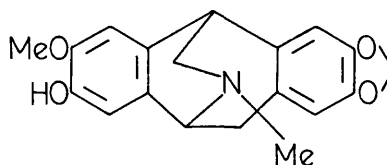
(44) R=CN

(53) R=H

mixture as before, and to remove the impurities from the phenolic bases by chromatography. This was achieved by stirring the bases in chloroform with silica, then filtering. Removal of the solvent afforded the pavine (54) (15%), which was recrystallised from acetone. Methanol washings of the silica



(54)



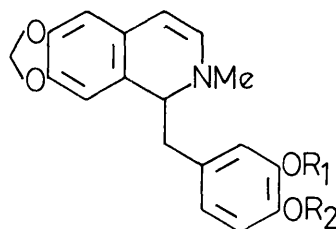
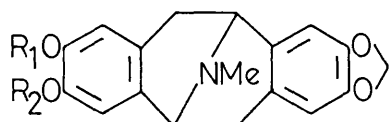
(6h)

were chromatographed on alumina to afford the isopavine (6h) in 9% yield. The microanalytical and spectral data (for N.M.R. spectra see page 154) were in accord with these assignments of structures, the characteristic mass spectral fragmentation pattern (see page 154) being the most useful means of differentiation. It was noted, that the two pavines (51) and (54) exhibited u.v. spectra in ethanol which were very similar to those of the isopavines (6g) and (6h), and that all four compounds show bathochromic shifts in the presence of alkali. However, the

spectra of the two pavines in hexane were resolved in the 290nm region into five peaks³⁹, whereas the isopavine compounds did not exhibit this phenomenon.

3. The alkaloid Caryachine: structure (51) or (54)?

The alkaloid caryachine was isolated by Japanese workers⁴⁰ in its racemic and optically active forms and was assigned the structure (51) or (54) on the basis of degradative and spectral studies. At the time of completion of this section of the



(51) $R_1 = H, R_2 = Me$

(55) $R_1 = CH_2Ph, R_2 = Me$

(54) $R_1 = Me, R_2 = H$

(56) $R_1 = Me, R_2 = CH_2Ph$

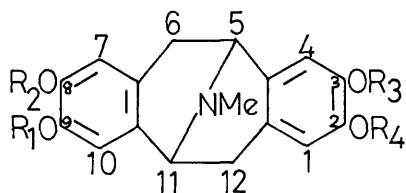
thesis two Indian workers reported⁴¹ the synthesis of these two pavines by cyclisation of the 1,2-dihydroisoquinolines (55) and (56) with a phosphoric acid and formic acid mixture. The pavine (51) was shown by melting point ($239-41^{\circ}$), mixed melting point, T.L.C., N.M.R., I.R. and U.V. to be identical with the naturally occurring dl-caryachine. The T.L.C. characteristics, N.M.R. and U.V. spectra of the alternative structure (54) (melting point $195-6^{\circ}$) were also identical with those of the

racemic alkaloid, but its I.R. spectrum showed slight differences.

The pavine (51) prepared herein by the aminonitrile route has a melting point of $240-1^{\circ}$, and an N.M.R. spectrum the same as that reported for the alkaloid caryachine. Isomer (54) however, prepared by this route has a melting point of $206-7^{\circ}$ ⁴¹ which is higher than that quoted by Natarajan and Pai⁴¹. The N.M.R. spectra of the two isomers prepared here, were obtained in four different solvents and are reproduced on page 153, where it can be seen that in the aromatic region there are significant differences in the two spectra, which is contrary to the report by the Indian workers, who, unfortunately do not quote the N.M.R. solvent used.

N.M.R. spectra of pavines.

In the light of a recent publication⁴² it seems unlikely that the N.M.R. spectra of the two pavines (51) and (54) would be identical. In this paper, Chen and Soine firstly proposed a new nomenclature for pavines, namely the "pavinane" ring system shown below and then studied the N.M.R. spectra in D.M.S.O. of the tetrasubstituted pavinanes (57 a-g). Data⁴³ for eschscholtzine (57h) and eschscholtzidine (57i) are included here to extend the study to methylenedioxy substituted pavinanes.



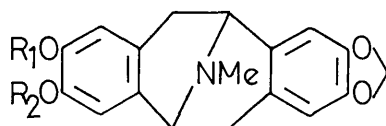
- | | |
|---------------------------------|--------------------------------------|
| a. $R_1=R_3=H$, $R_2=R_4=CH_3$ | f. $R_1=R_2=R_3=R_4=CH_3$ |
| b. $R_1=R_3=CH_3$, $R_2=R_4=H$ | g. $R_1=R_2=R_3=R_4=H$ |
| c. $R_1=R_4=H$, $R_2=R_3=CH_3$ | h. R_1R_2 and $R_3R_4=OCH_2O$ |
| d. $R_1=H$, $R_2=R_3=R_4=CH_3$ | i. $R_1R_2=OCH_2O$, $R_3=R_4=OCH_3$ |
| e. $R_2=H$, $R_1=R_3=R_4=CH_3$ | |

In argemonine (57f) the aromatic region of the N.M.R. spectrum shows two singlet absorptions at 6.54 and 6.78 δ . It was argued that H_4 and H_{10} appeared together as the lower field singlet due to deshielding by the inductive effect of the C-N bridge. This argument is not consistent however with the observed spectrum of the methohydroxide of argemonine⁴⁴ which would exert a larger inductive effect but exhibits aromatic absorptions in its N.M.R. spectrum very similar to those of argemonine. Similarly though, Chen and Soine argued that the methoxy groups at C_2 and C_8 appear about 0.1 ppm upfield compared with those at C_3 and C_9 . It seems much more likely however, from the observed chemical shifts, that anisotropic shielding rather than deshielding is predominant. A study of molecular models of this system shows that shielding by the aromatic rings is such that H_1 and H_7 are more shielded than H_4 and H_{10} . This

explains not only the non equivalence of the methoxy groups but that of the hydrogen atoms of the methylenedioxy functions which appear typically as two doublets in the 5.9δ region.

Chen and Soine advanced additivity rules to predict aromatic signal positions for the pavinane series, which when applied to the spectra of (51) and (54) gives good agreement with the observed spectra, obtained in this thesis.

Table 1



(51) $R_1 = H$, $R_2 = Me$

(54) $R_2 = H$, $R_1 = Me$

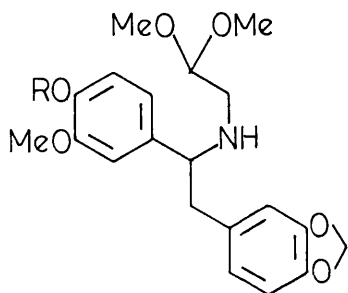
		δ values aromatic H (integral)			
		H_4	H_{10}	H_1	H_7
51	Found	6.75(1),	6.72(1),	6.51(1),	6.39(1)
DMSO	Predicted	6.78	6.70	6.54	6.36
54	Found	6.75	6.58	6.51	6.51
DMSO	Predicted	6.78	6.57	6.54	6.48

The N.M.R. spectra in deuterochloroform, however, do not conform to this additivity rule and a closer examination suggests that on changing from dimethylsulphoxide to deuterochloroform as solvent results in a downfield shift of up to 0.1ppm for aromatic protons ortho to a phenolic group and a comparable upfield shift for protons meta to the hydroxy group. This supports earlier studies with phenolic compounds³⁹, and serves to confirm the proton assignments made in table 1.

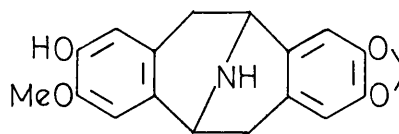
Further confirmation of pavine structures (51) and (54)

The structure relationship between the two pavines (51) and (54) was further confirmed when each was treated with diazomethane followed by methyl iodide to give two products which were shown by melting point, mixed melting point and infrared spectral comparisons to be identical.

Formation of the pavines in the reactions discussed is surprising, as no similar cyclisation has been observed in any previous acetal cyclisation of this type^{4,14,23}; isopavine is invariably formed. This point is discussed further on page 143. It is interesting to find that cyclisation of the acetal (58a) formed from the Schiff's base described on page 118, afforded even better (40%) yields of the pavine (59). The elemental analysis and N.M.R. spectrum (p. 164) obtained on this cyclisation product are consistent with this structure and the mass spectrum shows base peaks due to the isoquinolyl cations (60) and (61). Chromatographic separation of the mother liquors afforded a small

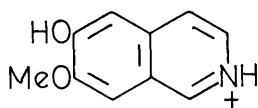


(58) a R=benzyl b R=H

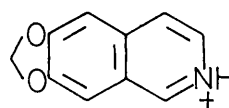


(59)

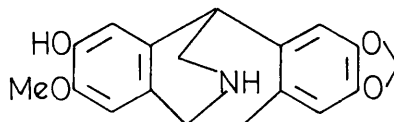
amount of a second phenolic base whose I.R. and U.V. spectra were similar to those of the pavine (59). The mass spectrum of this material, however, showed a molecular ion peak at 311m/e with a prominent loss of 29 m/e which is consistent with the isopavine (62) bridge loss of $(\text{CH}_2=\text{NH}^+)$.



(60)



(61)

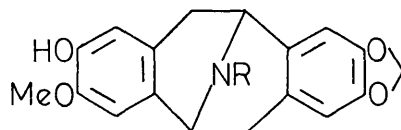


(62)

Although the base peak was as expected for (62) at 176 m/e, the 174 m/e peak was 20% of its size which suggested that it arose from the presence of (59) as an impurity. All attempts to obtain pure isopavine (62) failed.

Attempts to N-methylate pavine (59)³.

Compound (59) is the only known NH pavine other than pavine itself^{2,3} and in order to identify it with dl.caryachine (51)



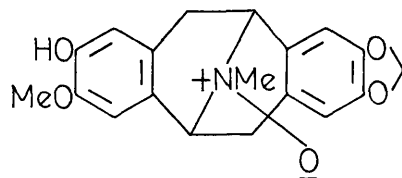
(59) R=H

(51) R=Me

N-methylation with formaldehyde followed by sodium borohydride was attempted. However, although a variety of conditions were tried, incomplete conversion was indicated by T.L.C., I.R. and mass spectrometric examination of the product. This is surprising, as this procedure has been employed successfully in the N-methylation of isopavines²³.

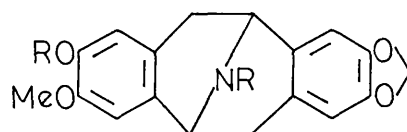
N-demethylation of caryachine (51).

An alternative approach was considered which is based on a method used for N-demethylation of some aporphine alkaloids⁴⁴, and involves treatment of the N-oxide with sulphur dioxide⁴⁵ followed by acid hydrolysis of the intermediate. This technique has not been reported in pavine series. Treatment of the N-oxide (63)⁴⁶, however, according to the described conditions resulted in the regeneration of the pavine (51).



(63)

A second method used to prepare pavine from its N-methyl parent argemonine⁴⁷ has also achieved success in the N-demethylation of morphine and related compounds⁴⁸. This involves treatment of the N-methyl alkaloid with ethyl chloroformate in chloroform and potassium carbonate to afford the N-carbalkoxy derivative. Subsequent hydrolysis gives the NH compound. In this way the pavine derivative (64) was prepared, prolonged treatment of which



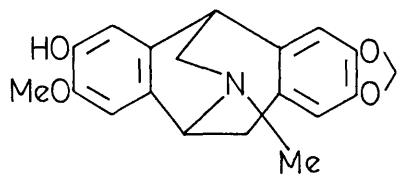
(64) R = COOEt

(59) R = H

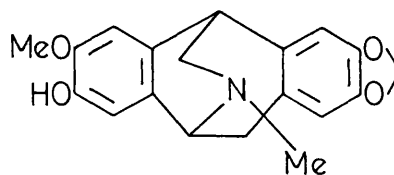
with 50% caustic soda at steam bath temperature afforded a crystalline solid, which was shown by T.L.C., melting point, mixed melting point and I.R. to be identical with (59).

Reframoline

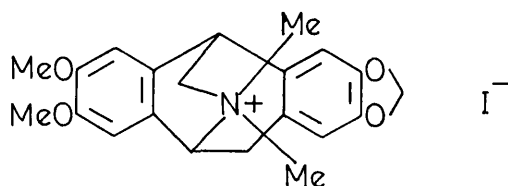
The two isomeric isopavines (6g) and (6h) were both treated with diazomethane followed by methyl iodide to afford the same methiodide (I.R. m.pt and mixed m.pt) which was shown to be identical by melting point, mixed melting point and infrared spectrum with an authentic sample of reframine methiodide (65)



(6g)



(6h)



(65)

The spectral characteristics of the two phenolic isopavines (6g) and (6h) were very similar and agreed with those reported for reframoline¹⁰(p154). In the aromatic region of the N.M.R. spectra of (6g) and (6h) there were slight differences, see table 2. In view of the unsymmetrical nature of the isopavine ring system, any such additivity rule for aromatic proton N.M.R. absorptions as that discussed for pavinanes would be more

Table 2.

Isomer	Solvent	Aromatic H δ (ppm)			
6g	CDCl ₃	6.75	6.75	6.63	6.50
	DMSO	6.89	6.81	6.72	6.58
	CD ₃ COCD ₃	6.90	6.76	6.68	6.46
6h	CDCl ₃	6.70	6.70	6.62	6.46
	DMSO	6.83	6.78	6.72	6.53
	CD ₃ COCD ₃	6.88	6.79	6.70	6.48

complicated. No firm proton assignments could be made in the aromatic region of these compounds despite comparisons with the collated data shown in table 3. In most cases the aromatic protons appear as three or four singlet absorptions due to the aromatic shielding effect discussed earlier. From a scale model of the isopavine system, table 4 was constructed which gives some indication of the relative shielding effects on protons H_A, H_B, H_C and H_D by the rings E and F.

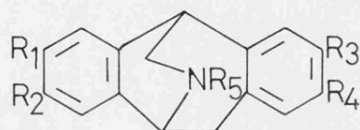


Table 3.

	R ₁	R ₂	R ₃	R ₄	R ₅	Aromatic protons (CDCl ₃ δ ppm)				Ref
Amurensine	OCH ₂ O		OMe	OH	Me	6.40*	6.72*	6.80*	6.80*	31,6
						6.53	6.58	6.70	6.70	
Amurensinine	OCH ₂ O		OMe	OMe	Me	6.53	6.63	6.63	6.73	6
Isoamurensine	OCH ₂ O		OH	OMe	Me	6.50*	6.58*	6.77*	6.80*	31
Reframine	OMe	OMe	OCH ₂ O		Me	6.55	6.70	6.83	6.90	23
Reframidine	OCH ₂ O		OCH ₂ O		Me	6.55	6.65	6.75	6.75	23
O-methylthalisopavine	OMe	OMe	OMe	OMe	Me	6.51	6.64	6.75	6.75	23
Thalisopavine	OMe	OMe	OMe	OH	Me	6.54	6.61	6.75	6.75	14
* in DMSO										

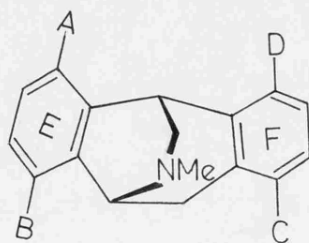


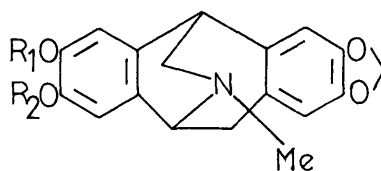
Table 4.

	Approximate distance Å	Angle included by a plane DFC and a line AF or BF
		<u>or</u> Angle included by a plane AEB and a line ED or EC
E - C	5.6	40°
E - D	4.8	15°
F - A	4.5	30°
F - B	5.9	15°

From table 4 an order of shielding is suggested below for aromatic protons in the isopavine system.

Proton	B		
	D	very little shielding	
	A	upfield $\approx 0.12 \delta$ (cf pavine)	
	C		
			increased shielding

In order to decide which of the two isopavines (6g) and (6h) has the structure of the alkaloid reframoline, a sample



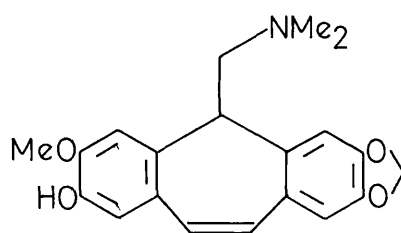
(6g) $R_1=H, R_2=Me$

(6h) $R_1=Me, R_2=H$

of each was sent to Professor Slavik¹⁰ for comparison studies. Compound (6g) was shown to be identical by I.R. to reframoline whereas the I.R. spectrum of (6h) showed differences. T.L.C. comparisons using three separate mixed solvent systems confirmed that (6g) is identical to reframoline and (6h) is different.

Hofmann degradation of isopavines (6g) and (6h)

Whilst these comparisons were being made a Hofmann degradation study of the two compounds was undertaken. The methiodide of (6h) was degraded smoothly into the methine base (66) which was obtained as a crystalline solid analysing for $C_{19}H_{21}NO_4$. Its

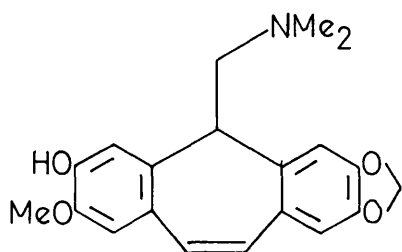


(66)

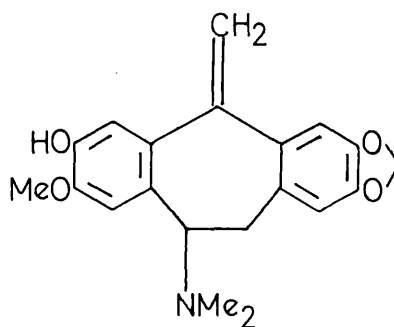
mass spectrum showed a molecular ion at 339 m/e accompanied by a typically intense peak at 281 m/e with a corresponding metastable transition for the loss of $CH_2=N^+(Me)_2$ ¹⁴. The N.M.R. spectrum corroborates this structure and is reproduced on page 156.

The u.v. spectrum is similar to that of analogous methine bases¹⁴ and shows very little bathochromic shift on the addition of alkali.

Similar treatment of the methiodide salt of (6g) afforded a pale yellow solid with a melting range of 152-8°. This material exhibited very similar M.S., I.R. and u.v. spectra to those shown by (66). The N.M.R. spectrum, however, although similar to that of (66) showed an additional methylenedioxy group, as an impurity. From the remainder of the spectrum it appeared that in addition to (67) the alternative methine base (68) was present. This is supported by the mass spectrum at low



(67)



(68)

electron voltage which shows only one molecular ion at the expected m/e value of 339. Satisfactory elemental analysis were obtained for nitrogen and hydrogen but the carbon analysis was 0.6% lower than the calculated value. This sample could not, however, be purified further. Its u.v. spectrum was recorded

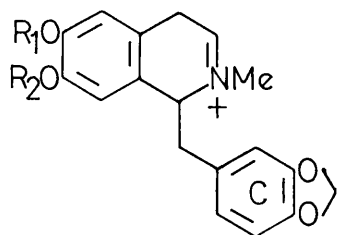
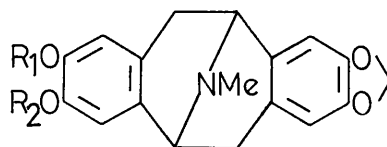
in ethanol, and showed a large bathochromic shift on the addition of sodium hydroxide. This is consistent with the extended conjugation of the phenate ion in (67) compared with that in (66), see page 156a.

Pavine versus isopavine formation

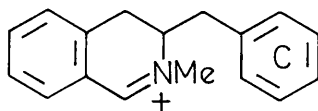
As discussed in scheme 2 page 104, nucleophilic displacement of the hydroxy group by the methylenedioxybenzyl group in a 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline would give rise to the isopavine system. Dehydration, on the other hand, followed by isomerisation to the 1,4-dihydroisoquinolinium salt and subsequent nucleophilic attack by the methylenedioxybenzyl grouping would afford the pavine ring system. These are competitive reactions and it is difficult to rationalise the relatively large amounts of pavines formed in the examples studied herein, when isopavines only have been previously reported. An investigation would be required under stringently controlled cyclisation conditions with an exhaustive examination of the reaction products in order to clarify these observations.

Evidence for a benzyl migration.

The intermediacy of the 1,4-dihydroisoquinolinium ions (69) and (70) has been demonstrated by the isolation of the pavines (51) and (54) from acetal cyclisations under acid conditions. As briefly discussed on page 19 and in detail in Chapter 3

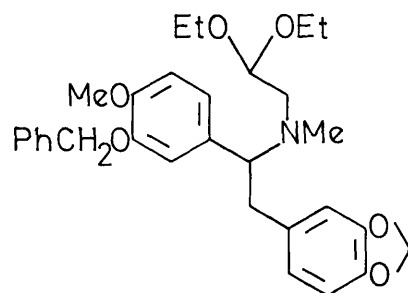
(69) $R_1 = \text{H or benzyl}$, $R_2 = \text{Me}$ (51) $R_1 = \text{H}$, $R_2 = \text{Me}$ (70) $R_1 = \text{Me}$, $R_2 = \text{H or benzyl}$ (54) $R_1 = \text{Me}$, $R_2 = \text{H}$

of this thesis, migration of the benzyl group from C_1 to C_3 can occur to form the 3-benzyl-3,4-dihydroisoquinolinium salt (71). It is known⁴⁹ that if ring C is substituted at C_3 and C_4 by



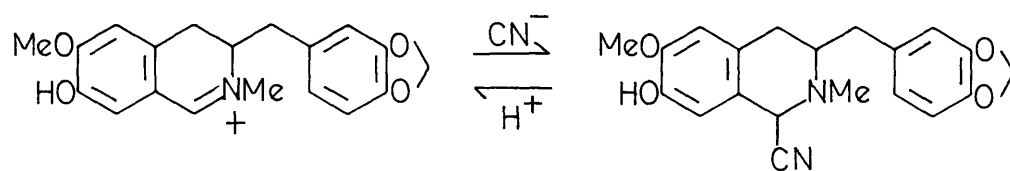
(71)

alkoxy groups there is an increased tendency for double cyclisation to the pavine system, over C_1 to C_3 migration. This is consistent with the yields of pavine formed by cyclisation through intermediates (69) and (70), and it was hoped that some migration product would be observed with the same system. To this end the acetal (40) was treated with



(40)

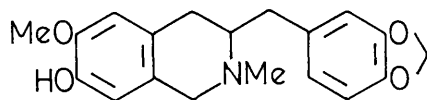
six normal hydrochloric acid at steam bath temperature and the solution basified with sodium bicarbonate, and extracted into chloroform. The organic extracts were washed with water and discarded. Treatment of the combined aqueous phase with sodium cyanide and extraction into ether afforded a small quantity of pale yellow solid. The U.V. spectrum of this product in acidified ethanol exhibited absorption maxima at 253, 315 and 374nm, typical of a 3,4-dihydroisoquinoline derivative. In ethanol alone, however, the spectrum was consistent with the equilibrium mixture of 1,2,3,4-tetrahydroisoquinoline and 3,4-dihydroisoquinoline, shown by the additional absorption at 289nm⁴⁹. This equilibrium is represented below.



(72)

The mass spectrum of this product (M^+ m/e 352) (72) showed a large peak at m/e 325, consistent with the loss of HCN from the molecular ion, and one at m/e 190 explained by the additional facile loss of the methylenedioxybenzyl grouping. This mass spectral fragmentation pattern is consistent with structure (72) and with those observed for authenticated compounds of this type described in chapter 3 of this thesis.

Reduction of this product with sodium borohydride, followed by isolation of phenolic basic material afforded an oil which exhibited a u.v. maximum at 294nm, typical of a tetrahydroisoquinoline. The mass spectrum showed a weak molecular ion at m/e 327, consistent with (73), and an intense peak at m/e 192 which was considered to be due to the facile loss of the methylene-



(73)

dioxy benzyl group from the molecular ion. These observations indicate that where C_1 to C_3 migration occurs it represents only a minor reaction pathway.

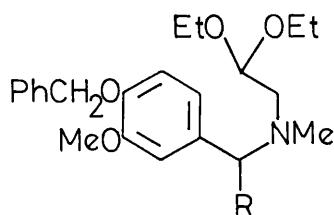
An interesting by-product from pavine and isopavine synthesis

The following observations concerning the aminonitrile route to the isopavine and pavine systems were made

(a) The mass spectra of bases containing isopavine and pavine from acetal cyclisation under shorter reaction times than normal (i.e. less than 1 hour), show some fragmentations typical of isopavine and pavine structures of molecular weight 415, 90 mass units higher than the expected phenolic pavine or isopavine. This indicates that ring closure can occur prior to cleavage of the benzyl ether grouping.

(b) The main impurity which hindered chromatographic separation of isopavine from pavine gives rise to a prominent peak in the mass spectrum at 192m/e.

In an attempt to isolate this impurity the bases from cyclisation of the acetal (39) contaminated with (47) were catalytically hydrogenolysed to remove any benzyl ethers and



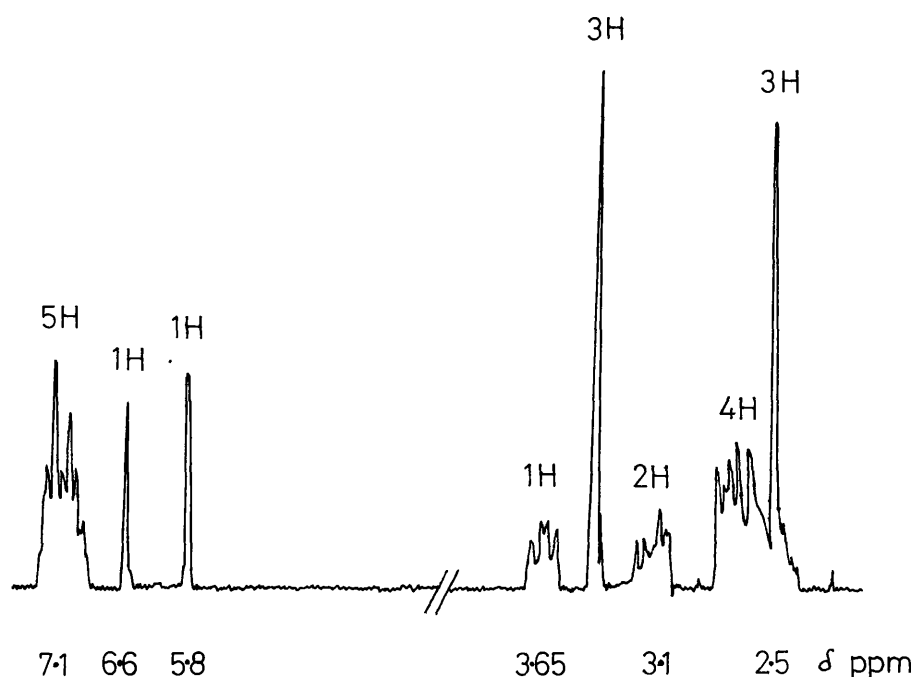
(39) R = 3,4-methylenedioxybenzyl

(47) $R = H$

chromatographed over silica to afford a new phenolic base, which showed in its mass spectrum the prominent peak at m/e 192. A

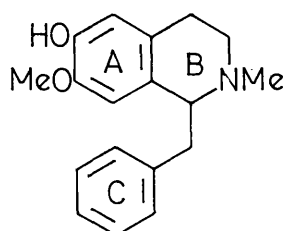
closer examination of the low electron voltage M.S. showed that this peak arose by loss of a benzyl group (m/e 91) from the molecular ion at m/e 283. A high resolution mass measurement of the molecular ion confirmed the molecular formula as $C_{18}H_{22}NO_2$. The u.v. spectrum was typical of a 1,2,3,4-tetrahydroisoquinoline, and this indication was supported by the N.M.R. spectrum (see fig 1) which showed a complex absorption due to six protons between 3.5 δ and 2.5 δ .

fig. 1

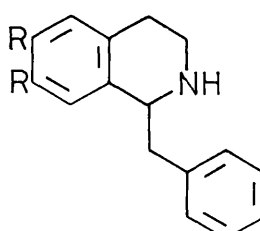


The data so far is consistent with that predicted for 1-benzyl-1,2,3,4-tetrahydroisoquinoline (74). Reported data⁵⁰, both N.M.R. and melting point, support this assignment. Although 1-benzylisoquinolines exist preferentially in the

conformation (75), it has been shown⁵¹ that in the corresponding N-methyl compounds there is sufficient steric repulsion to force ring C into a preferred conformation underneath ring A. This effect is reflected in the N.M.R. spectrum of (74) which shows C_8-H to be shielded so as to absorb at 5.83δ . The shielding effect on the aromatic methoxy group is also evident from its

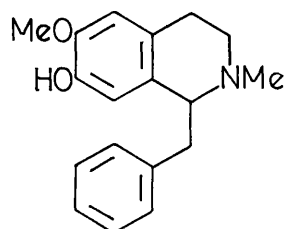


(74)



(75)

chemical shift of 3.44δ compared with 3.78δ for the corresponding

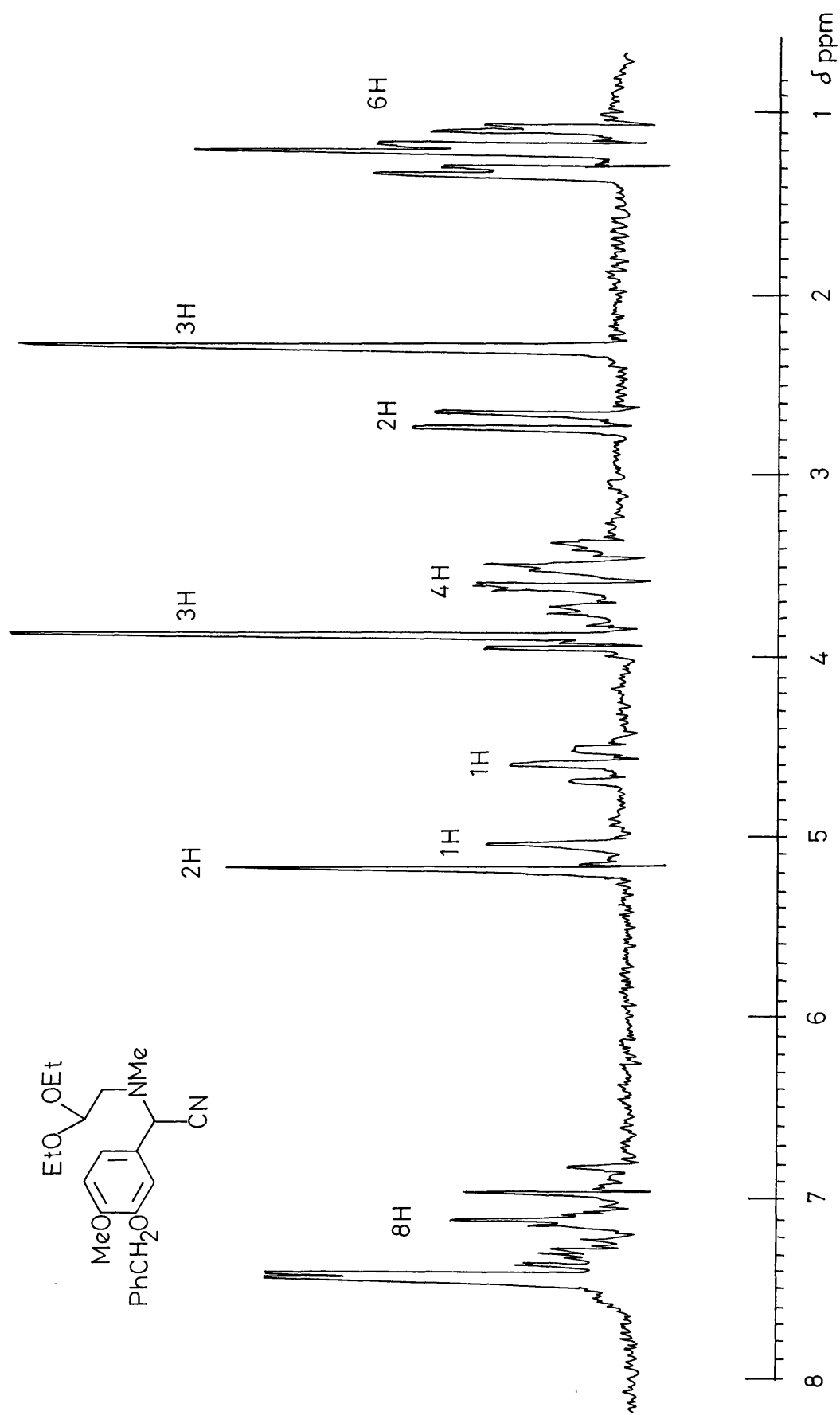


(76)

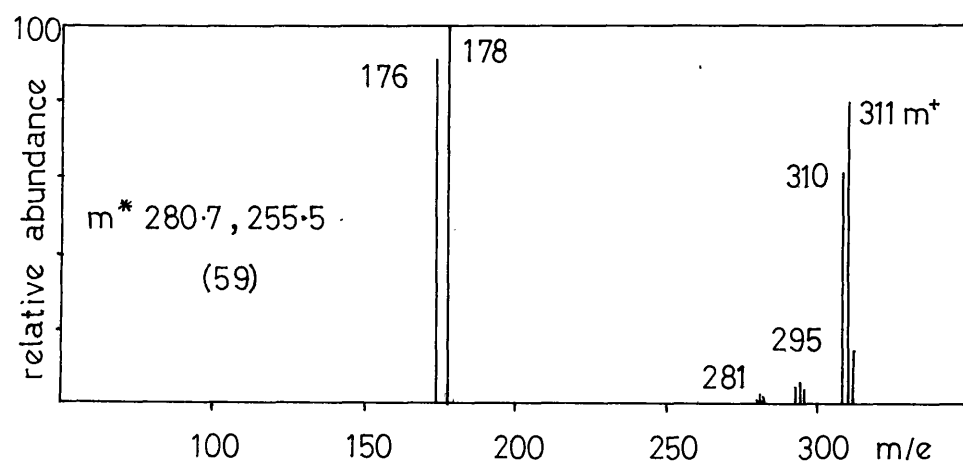
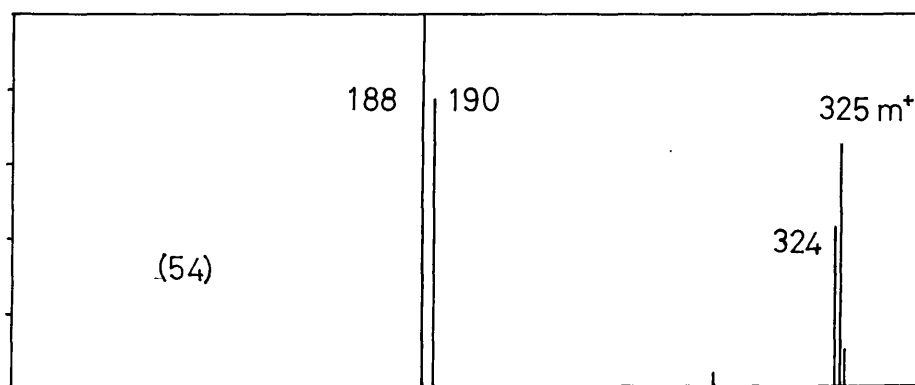
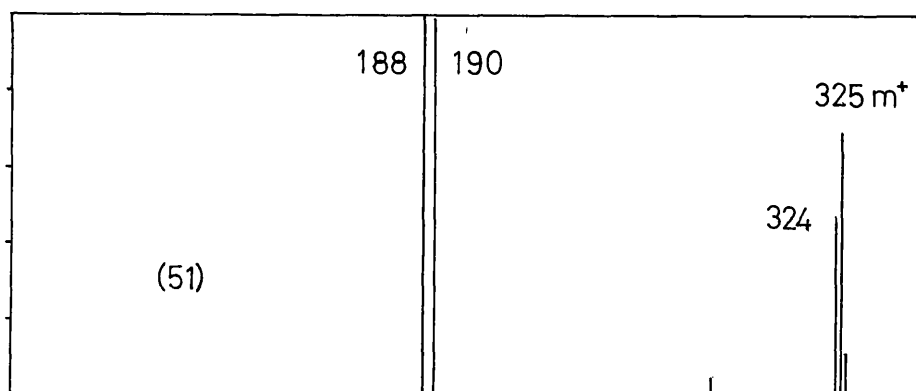
grouping in the isomer (76)⁵⁰.

The formation of the 1-benzylisoquinoline (74) is difficult to rationalise. As the next section of this work involves a brief study of the mechanism of benzyl migration from C₁ to C₃ in a 1,2-dihydroisoquinoline under acid conditions it seems a little disturbing to the author that a benzyl group has appeared to migrate, in a similar system, under similar conditions.

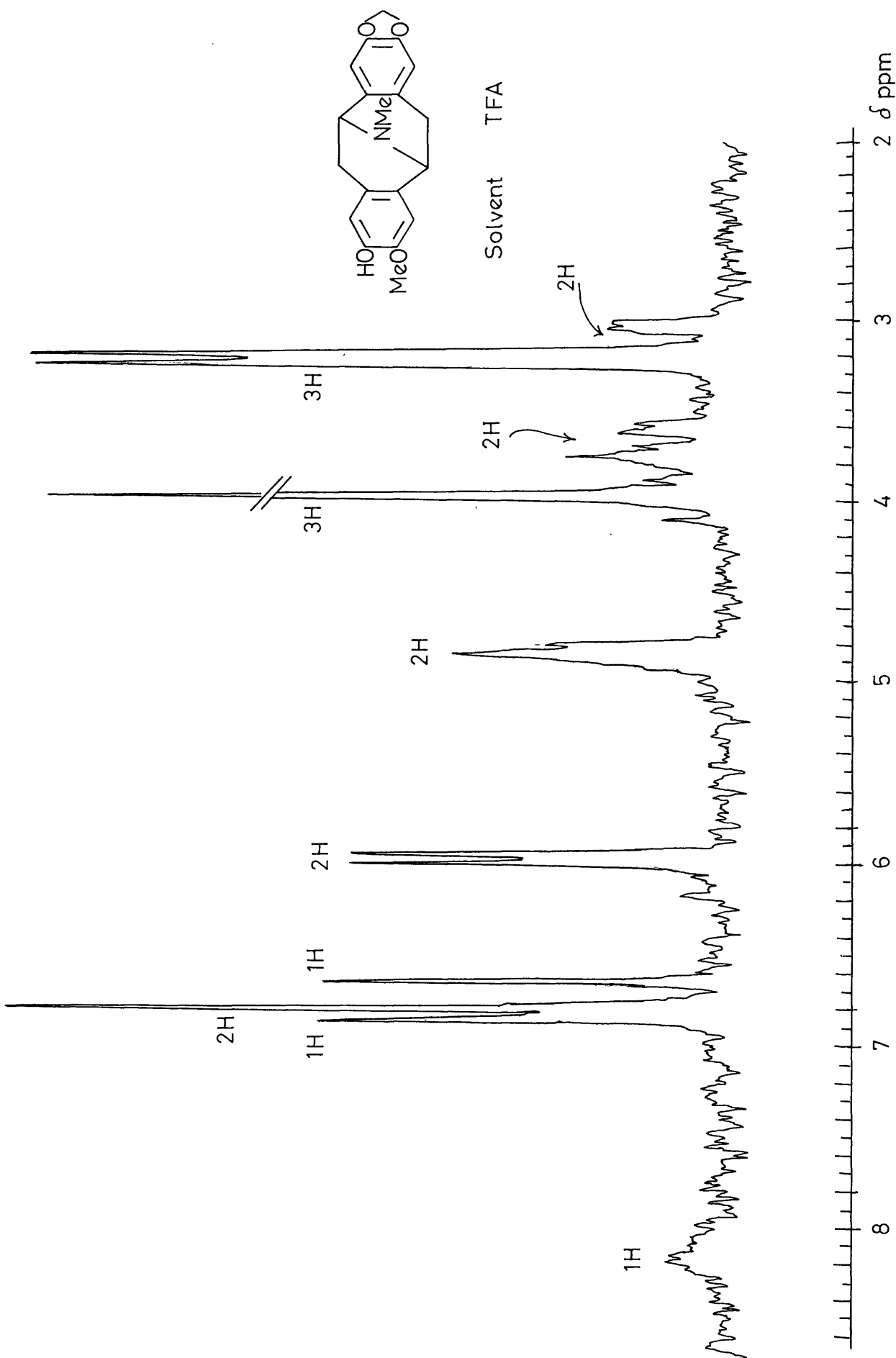
9. Spectra



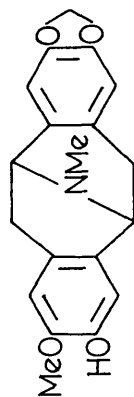
PAVINES



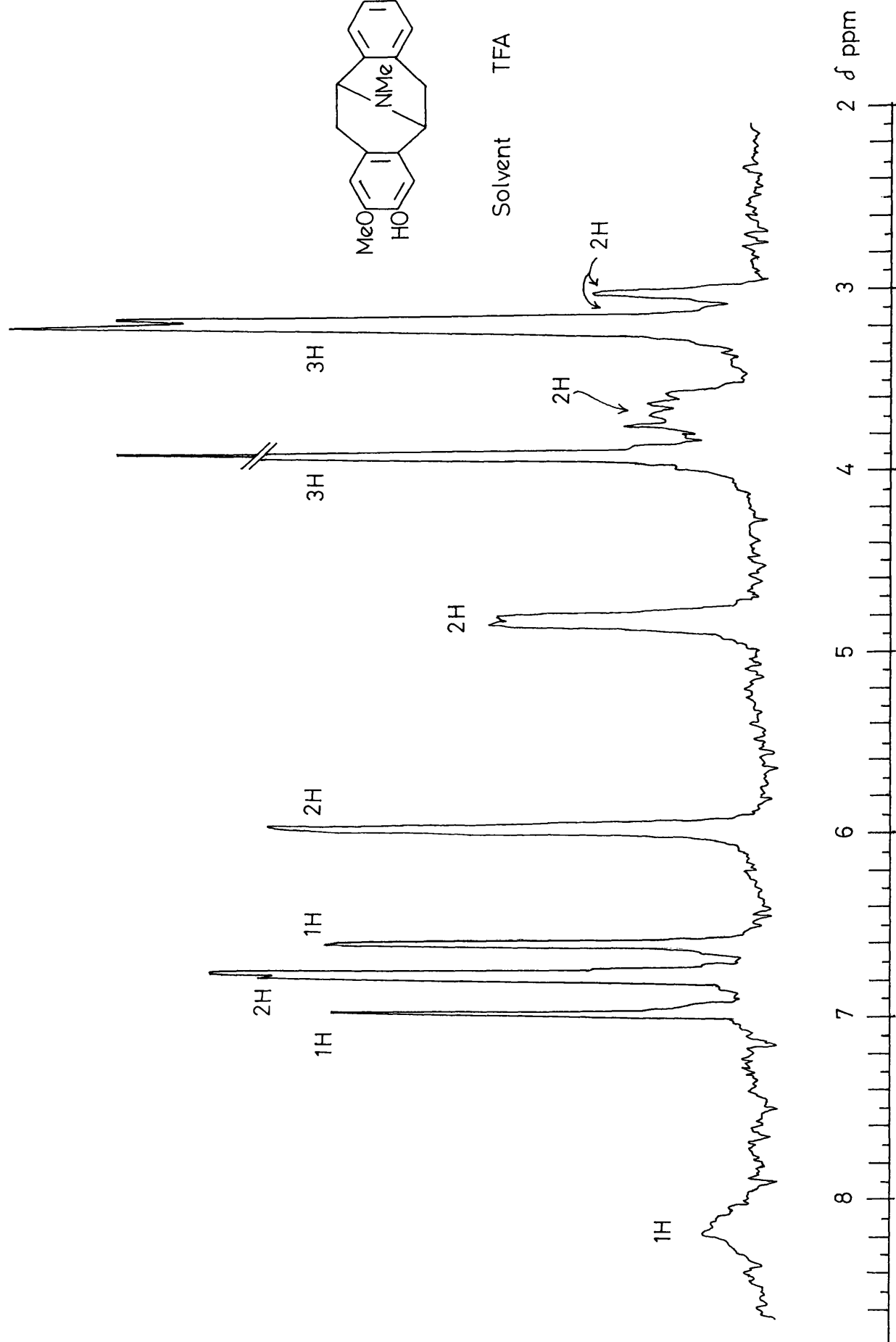
m^* metastable peaks



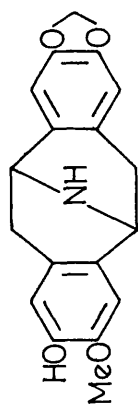
153a.



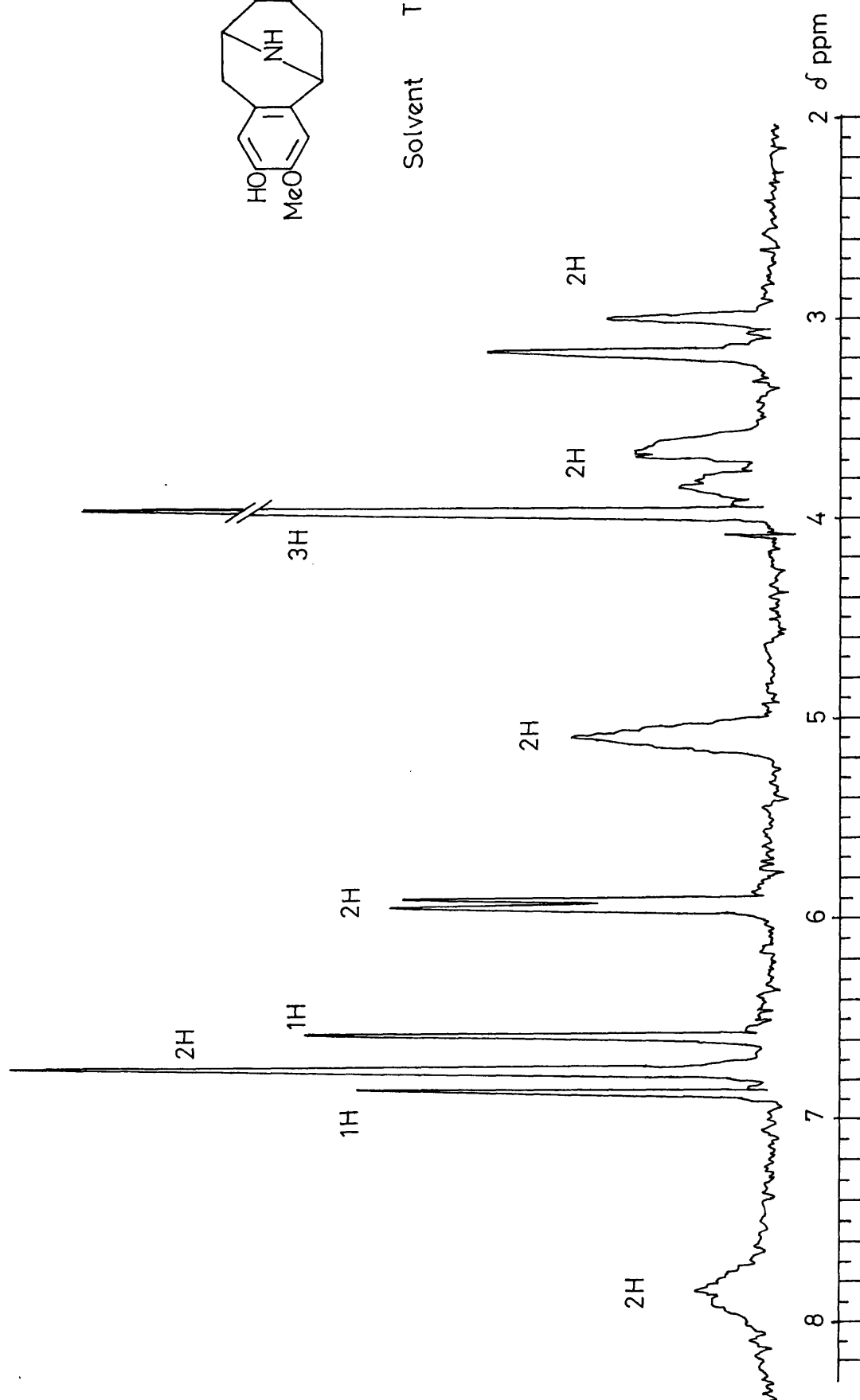
Solvent TFA



153b



Solvent TFA

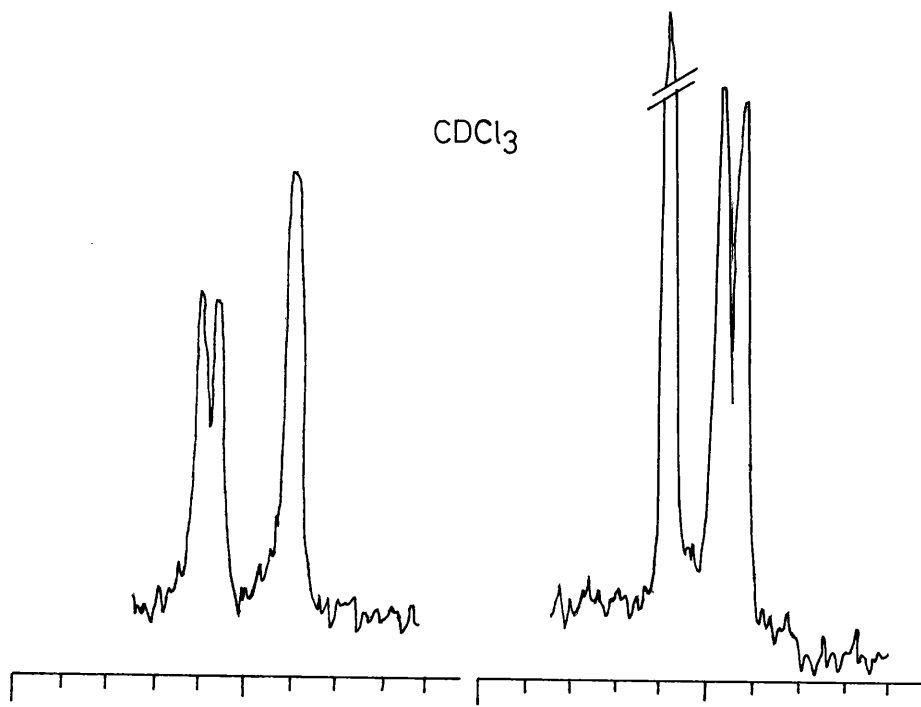


153c

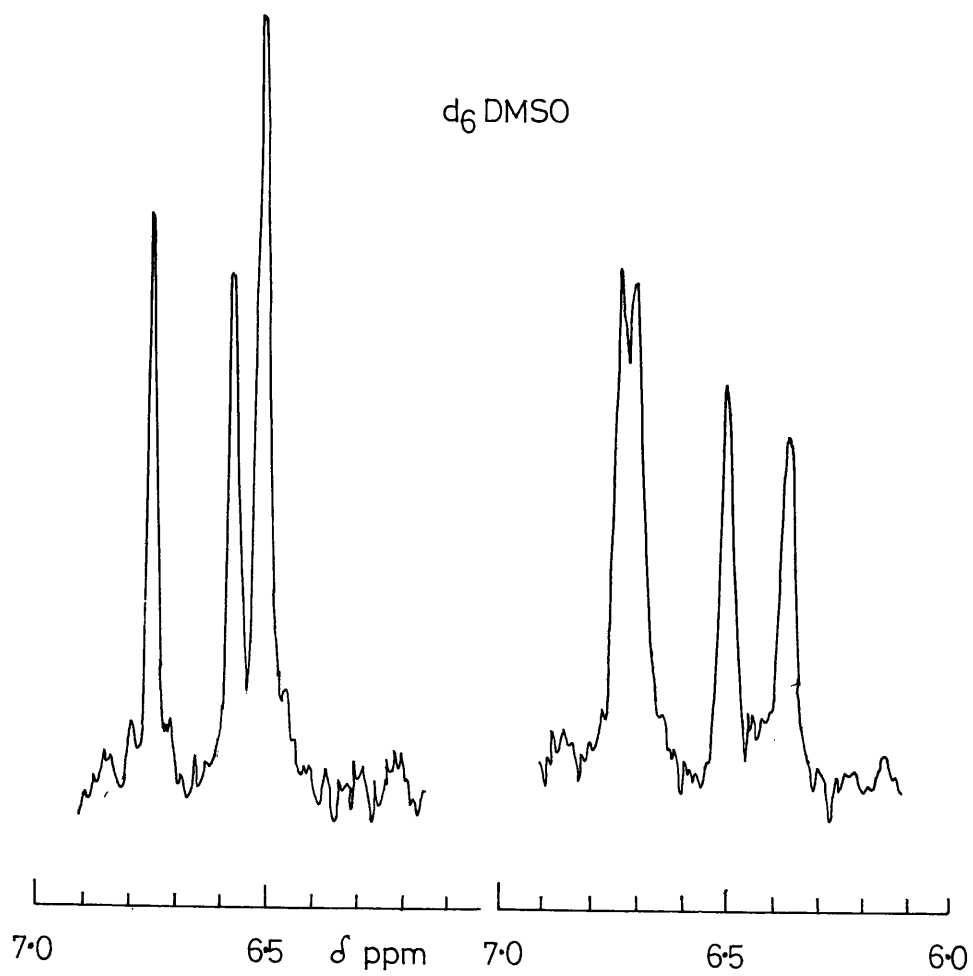
PAVINE (54)

PAVINE (51)

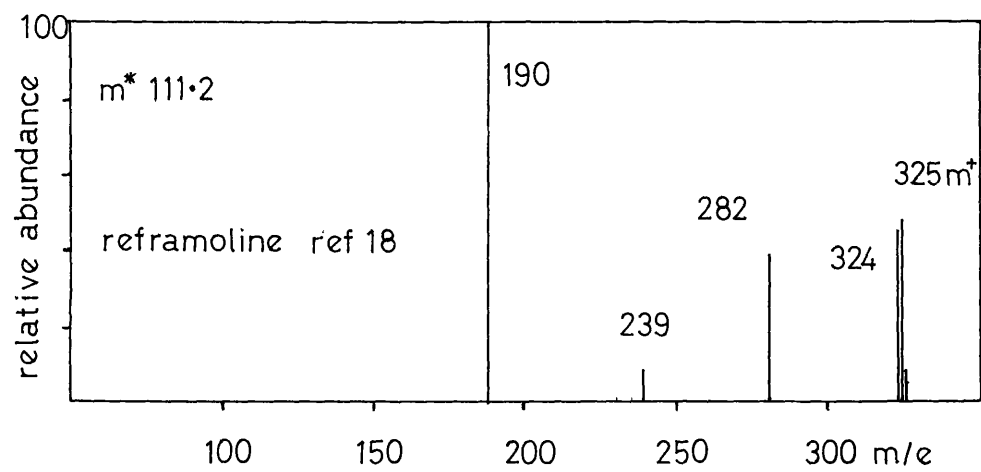
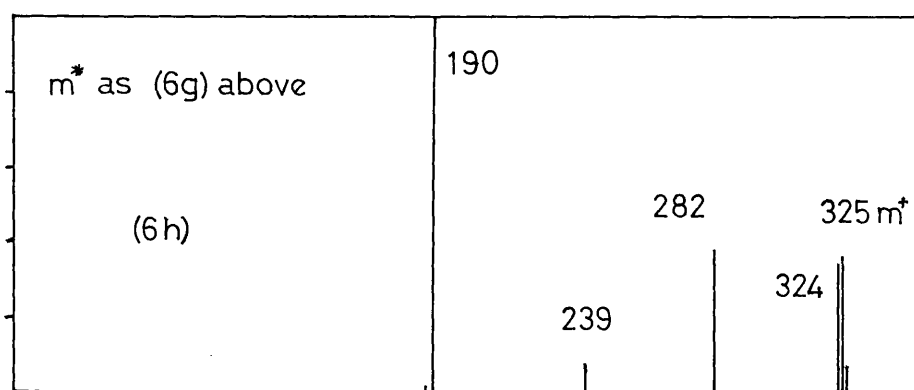
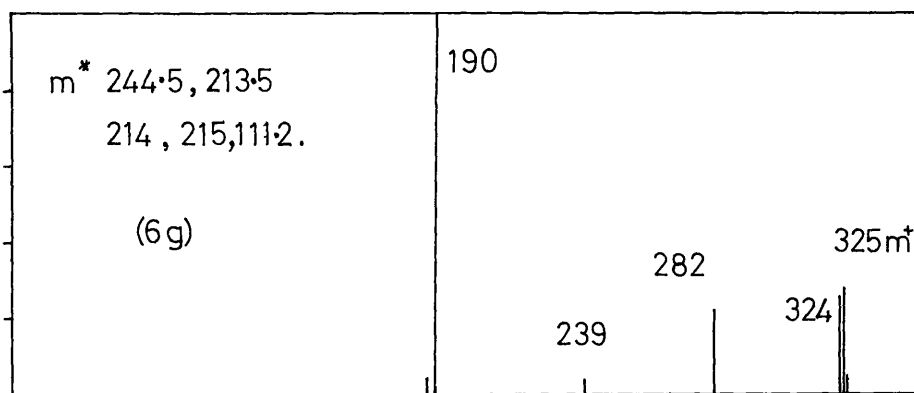
CDCl_3



d_6DMSO

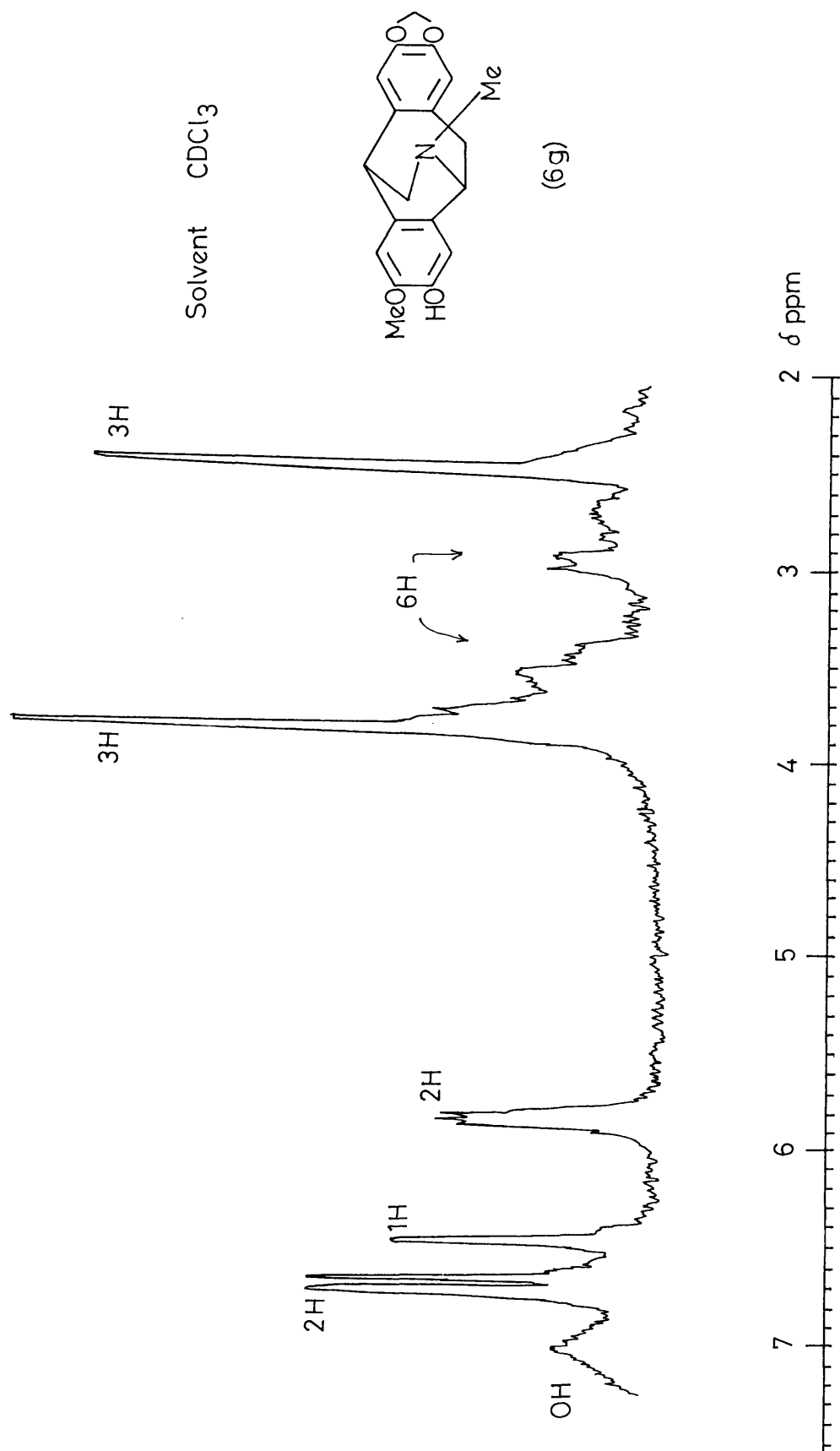


ISOPAVINES

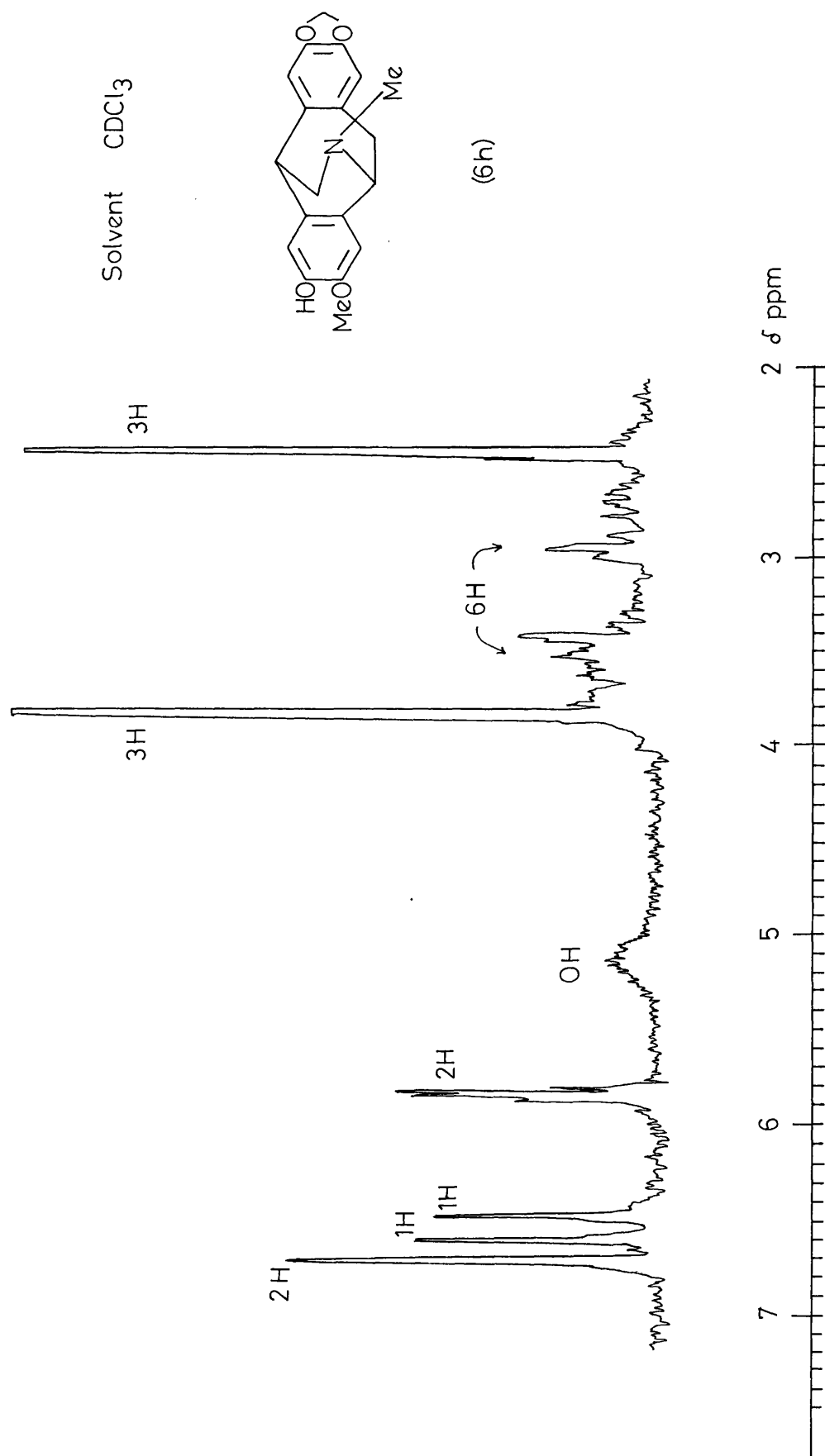


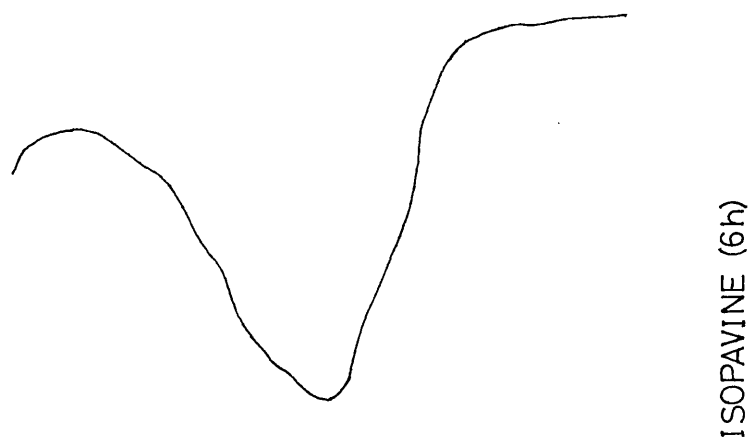
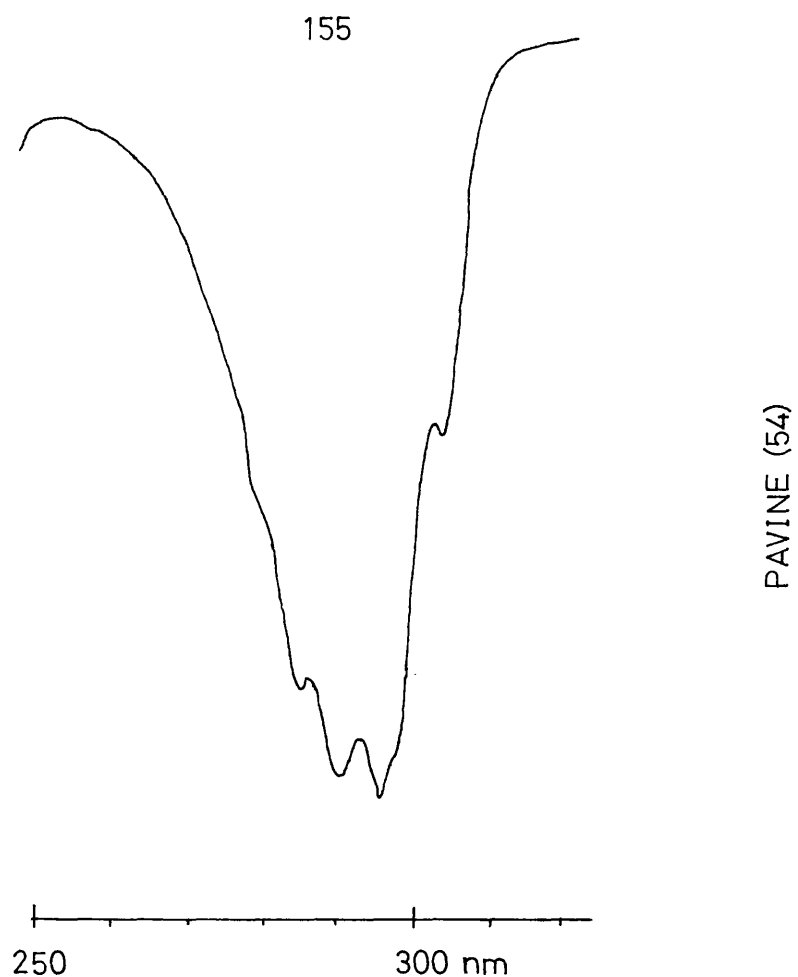
m^* metastable peaks

154a

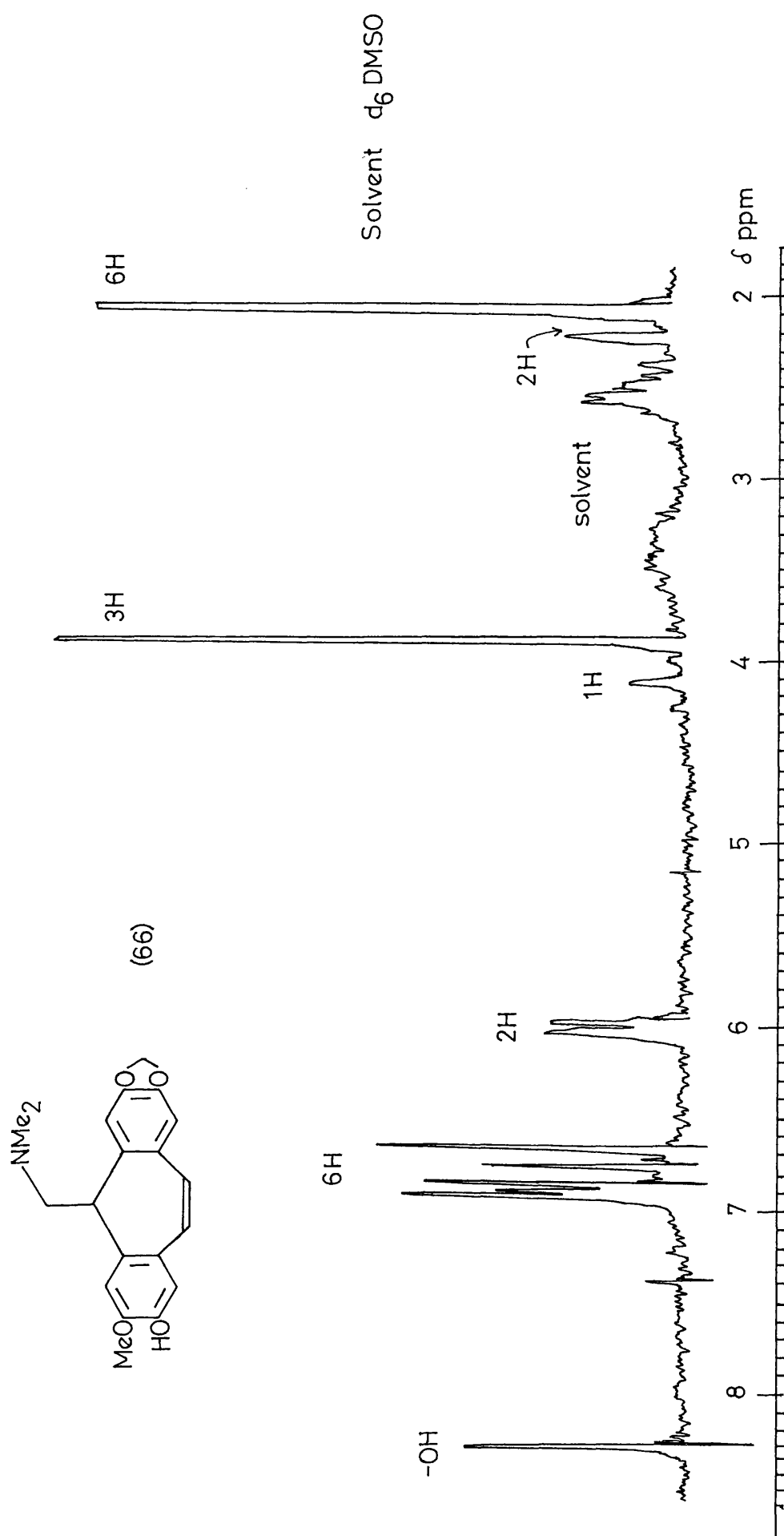


154b

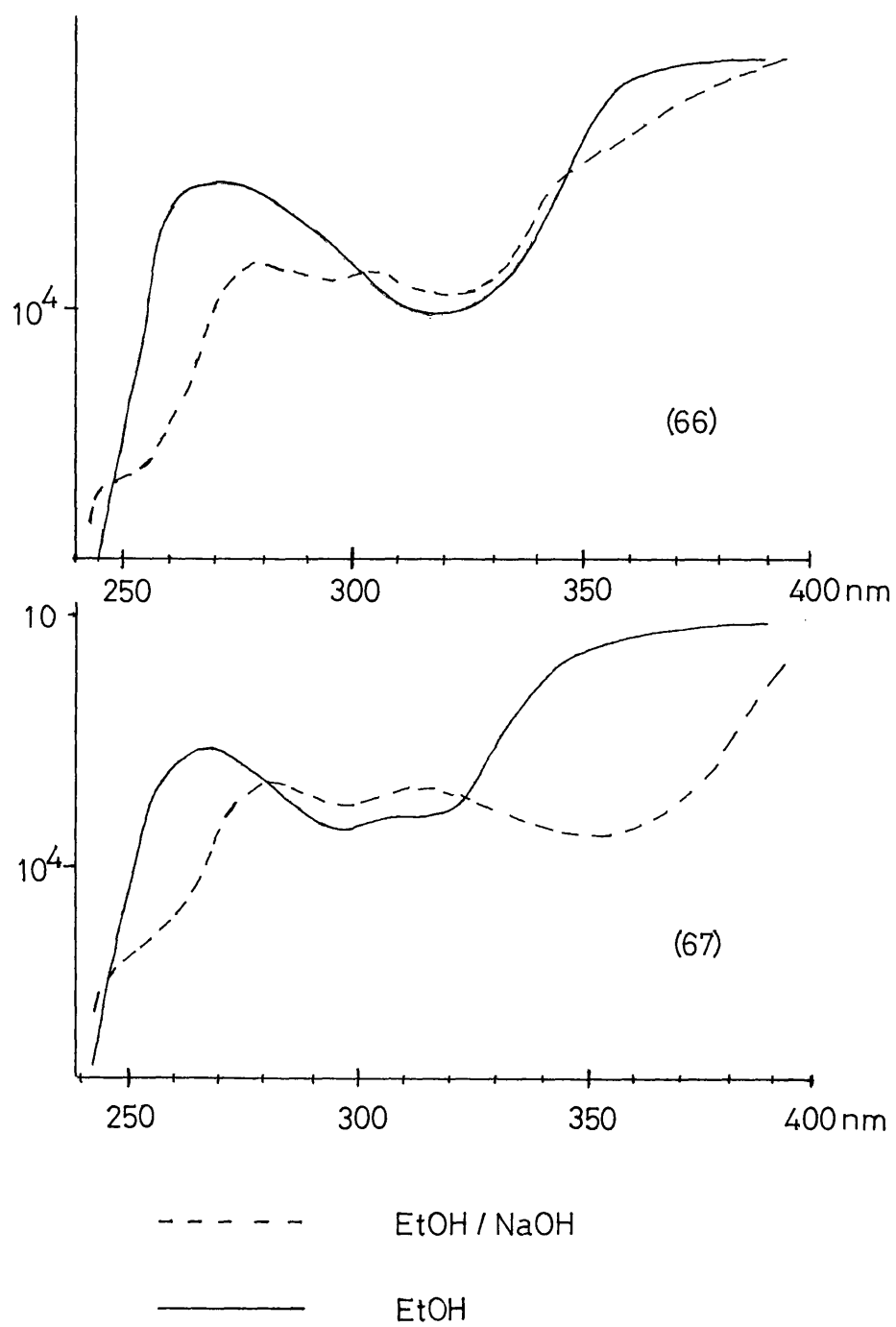




UV SPECTRA OF A PAVINE AND AN ISOPAVINE
SHOWING RESOLUTION IN HEXANE



UV SPECTRA OF METHINE BASES



10. Experimental

Preparation of the aminonitriles (32a-c).

The aldehyde (0.05 moles) in the minimum amount of MeOH was added over 1hr to a solution of diethylammonium chloride (0.06 moles) and NaCN (0.06 moles) in H₂O (10ml). The solution was stirred at 30° for 4 hr, quenched with H₂O (200ml) and extracted into ether (4 x 50ml). The combined ether extracts were washed with H₂O (4 x 20ml), saturated sodium metabisulphite soln (4 x 20ml), and water (2 x 20ml). After drying the ether extracts (MgSO₄) removal of the solvent afforded a pale yellow oil which solidified on standing (Yields 80-90%). (N.B. The benzyl ethers of vanillin and isovanillin are insoluble in sodium metabisulphite soln, so the reaction in these cases must remove all of the aldehyde. α-Cyano-N,N-diethyl-4-benzyloxy-3-methoxy-benzylamine (32a) (13.9g, 86%), m.p. 68-9° (petrol) N.M.R. (CDCl₃) 7.5-6.8 complex [8] (aromatic H), 5.12 s [2] (PhCH₂O), 4.93 s [1] (Ar-CH-CN), 3.87 s [3] (ArOCH₃), 2.59 q [2] J=7 Hz and 2.50 q [2] J=7 Hz (N-(CH₂-CH₃)₂), 1.05 t [6] J=7Hz (N(CH₂CH₃)₂); ν_{\max} (liquid film) 2230, 1598, 1514, 1274, 1150, 1035; λ_{\max} (ε) 232 (12,600), 280 (6,400), 311 (3,360); mass m/e 324 (M⁺) [22%], 252 [10%], 242 [8%], 207 [18%], 91 [100%]. (Found: C, 74.0; H, 7.3; N, 8.6. C₂₀H₂₄N₂O₂ requires: C, 74.1; H, 7.5; N, 8.6%).

α -Cyano-N,N-diethyl-3-benzyloxy-4-methoxybenzylamine (32b).

(12.9g, 80%), m.p. 57-8° (petrol) N.M.R. (CDCl_3) 7.6-6.8 complex [8] (aromatic H), 5.18 s [2] (PhCH_2O), 4.90 s [1] (ArCH-CN), 3.89 s [3] (ArOCH_3), 2.59 q [2] $J=7$ Hz and 2.50 q [2] $J=7$ Hz ($\text{N-(CH}_2\text{CH}_3)_2$), 1.02 t [6] $J=7$ Hz ($\text{N(CH}_2\text{CH}_3)_2$); ν_{max} (liquid film) 2220, 1597, 1515, 1273, 1148, 1030; λ_{max} (ϵ) 232 (10,000), 281 (3,340), 311 (900); mass m/e 324 (M^+) [16%], 252 [24%], 242 [9%], 207 [34%], 91 [100%]. (Found: C, 74.0; H, 7.5; N, 8.4. $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$ requires: C, 74.1; H, 7.5; N, 8.6%).

 α -Cyano-N,N-diethyl-3,4-dimethoxybenzylamine (32c) (10.9g, 88%)

as a pale yellow oil, N.M.R. (CDCl_3) 7.1 s [1] ($\text{C}_2\text{-H}$), 6.88 d [1] $J=8$ Hz and 7.15 d [1] $J=8$ Hz ($\text{C}_5\text{-H}$ and $\text{C}_6\text{-H}$), 4.98 s [1] (Ar-CH-CN) 3.90 s [6] (2 x ArOCH_3), 2.64 q [2] $J=7$ Hz and 2.55 q [2] $J=7$ Hz ($\text{N-(CH}_2\text{CH}_3)_2$), 1.10 t [6] ($\text{N(CH}_2\text{CH}_3)_2$); ν_{max} (liquid film) 2230, 1597, 1515, 1150, 1034; mass m/e 248 (M^+) [11%], 176 [100%], 166 [33%], 151 [33%].

An attempt to prepare (32d) by the same procedure from vanillin afforded only a dark uncharacterised liquid.

The bisulphite method of formation of aminonitriles.

The method according to Luten^{34d}, which involves addition of the amine to vanillin o-benzyl ether in sodium bisulphite soln. returned unreacted aldehyde in 92% yield.

Preparation of deoxybenzoins (33a-f) using NaH and D.M.F:General method.

Sodium hydride (60% suspension in oil, 0.02 moles NaH) was washed with petrol and suspended in dry DMF (10ml) under N_2 .

A solution of the aminonitrile (32a,b,c) (0.015 moles) in dry DMF (20ml) was added. The resulting red suspension was stirred under N_2 at R.T. for 1hr. and the benzylchloride (0.015 moles) added over a further hr. After stirring overnight the excess NaH was destroyed with MeOH (5ml) and the solvent removed under lmm. pressure, at 90° over 6hr. The resulting red oil was stirred in 6N HCl for 16 hr. and extracted into $CHCl_3$ (3 x 30ml). The combined $CHCl_3$ extracts were washed with H_2O (2 x 20ml), dried ($MgSO_4$) and evaporated to leave an oil. In each case the deoxybenzoins crystallised on trituration with ether. Reaction of the aminonitrile (32a) with 3,4-methylenedioxybenzyl chloride gave 4-benzyloxy-3-methoxyphenyl 3,4-methylenedioxybenzyl ketone (33b) (61%) m.p. $98-9^\circ$ (MeOH) N.M.R. ($CDCl_3$) 7.7-6.6 complex [11] (aromatic H), 5.89 s [2] ($O-CH_2-O$), 5.20 s [2] ($Ph-CH_2O$), 4.10 s [2] ($ArCH_2CO$), 3.89 s [3] ($ArOCH_3$); ν_{max} 1668, 1602, 1591, 1275; λ_{max} (ϵ) 315sh (11,000), 280 (16,000), 232 (28,400); mass m/e 376 (M^+) [3.3%], 241 [50%], 135 [18%], 91 [100%], metastable 154.5. (Found: C, 73.5; H, 5.4. $C_{23}H_{20}O_5$ requires: C, 73.4; H, 5.4%).

Similarly from the aminonitrile (32b), 3-benzyloxy-4-methoxyphenyl 3,4-methylenedioxybenzyl ketone (33c) (74%) was prepared as white crystals from EtOH, m.p. $144-5^\circ$. NMR ($CDCl_3$) 7.75-6.7 complex [11] (aromatic H), 5.90 s [2] (OCH_2O), 5.17 s [2] ($PhCH_2O$), 4.08 s [2] ($ArCH_2CO$), 3.90 s [3] ($Ar-OCH_3$); ν_{max} 1670, 1598, 1586, 1270; λ_{max} (ϵ) 320sh (8,100), 282 (11,600), 232 (26,000);

mass m/e 376 (M^+) [3.5%], 241 [33%], 135 [5.5%], 91 [100%].

(Found: C, 73.1; H, 5.6. $C_{23}H_{20}O_5$ requires: C, 73.4; H, 5.4%).

Also from the aminonitrile (32b) with 3,4,5-trimethoxybenzyl chloride, 3-benzyloxy-4-methoxy phenyl 3,4,5-trimethoxybenzyl ketone (33d) was obtained (63%) m.p. $131-2^\circ$. N.M.R. ($CDCl_3$) 7.8-6.8 complex [8] (aromatic H), 6.46 s [2] ($C_6H_2(OCH_3)_2$), 5.14 s [2] ($PhCH_2O$), 4.10 s [2] ($Ar-CH_2CO$), 3.90 s [3] ($ArOCH_3$), 3.80 s [6] ($2 \times ArOCH_3$); ν_{max} 1680, 1595, 1134, 1032; λ_{max} (ϵ) 232 (25,400), 280 (10,200), 310 (7,900) mass m/e 422 (M^+) [40%], 241 [100%], 181 [36%], 91 [100%], metastable 138.6 (Found: C, 71.0; H, 6.2. $C_{25}H_{26}O_6$ requires: C, 71.1; H, 6.2%).

From the aminonitrile (32c) with benzyl chloride, benzyl 3,4-dimethoxyphenyl ketone (33a) was obtained in 68% yield, m.p. $81.5-2^\circ$ (petrol) N.M.R. ($CDCl_3$) 7.31 s [5] ($C_6H_5CH_2$), 7.65 d [1] $J=8$ Hz (C_6H), 6.88 d [1] $J=8$ Hz (C_5H), 7.60 s [1] (C_2H), 4.23 s [2] ($PhCH_2CO$), 3.9 s [3] and 3.89 s [3] ($2 \times ArOCH_3$); ν_{max} 1678, 1519, 1243, 1148, 1033, 820, 730; mass m/e 256 (M^+) [11%], 165 [100%], 91 [5%].

Also from the aminonitrile (32c) with 3,4-dimethoxybenzyl chloride 3,4-dimethoxybenzyl 3,4-dimethoxyphenyl ketone (33c) was obtained (66%) m.p. 105° lit 107° , I.R. spectrum superimposable on that of authentic sample⁵². The alkoxy-substituted benzyl chlorides were prepared from the appropriate benzyl alcohol in $CHCl_3$ at $0-5^\circ$ with thionyl chloride (5 fold excess). After standing at this temperature overnight the solution was carefully washed with aqueous

NaHCO_3 soln, water and dried (MgSO_4). Evaporation of the solvent gave colourless products suitable for the above alkylations.

Preparation of 4-hydroxy-3-methoxyphenyl 3,4-methylenedioxybenzyl ketone (25b).

4-Benzyloxy-3-methoxyphenyl 3,4-methylenedioxybenzyl ketone (33b) (190mg) in 95% EtOH (50ml) over 10% Pd/C was hydrogenated at R.T., and atmospheric pressure for 1.5hr. After this time 14cc of H_2 had been consumed. Removal of the catalyst and solvent afforded the desired (25b) (125mg, 87%) m.p. $132-3^\circ$ (ether/EtOH) N.M.R. (CDCl_3) 7.7-6.72 complex [6] (aromatic H), 5.90 s [2] (OCH_2O), 6.1-5.5 broads (OH, removed by D_2O), 4.10 s [2] (ArCH_2CO), 3.88 s [3] (ArOCH_3); ν_{max} 3400 broad, 1672, 1494, 1268, 1253, 1162; λ_{max} (ϵ) 233 (19,500), 287 (13,00), 310sh (10,040); λ_{max} (ϵ) EtOH/NaOH 250 (10,000), 293 (6,360), 355 (26,000); mass m/e 286 (M^+) [10%], 151 [100%], 135 [12%]. Found: C, 66.9; H, 5.1; $\text{C}_{16}\text{H}_{14}\text{O}_5$ requires C, 67.1; H, 4.9%.

Attempted formation of (25b) from (33b) by acid treatment

(33b) (190mg), and 6N HCl (25ml) were heated together on a steam bath for 6hr. Extraction of the cooled mixture afforded unchanged (33b) (120mg, 64%) m.p. $97-8^\circ$.

Reaction of 3,4-dimethoxybenzyl 3,4-dimethoxyphenyl ketone (33c) with N-methylaminoacetaldehydediethylacetal.

(a) The ketone (33c) (850mg), with the acetal (2.1g) and p-toluene sulphonic acid (PTSA) (10mg) in toluene (100ml) was heated under reflux with a Dean and Stark for 20hr under an atmosphere of nitrogen. Removal of the solvent afforded starting

ketone (800mg).

(b) The ketone (33c) (700mg) and the acetal (1.9g) was stirred under N_2 with MeOH (10ml) and NaOH (2g). After 2.5 days the mixture was thrown into ether (200ml), dried ($MgSO_4$) and the solvent removed. Trituration of the residue over ether afforded starting ketone (500mg) and concentration of the ether washings afforded veratril (36) (78mg) m.p. $227-9^\circ$, lit⁴ 229° N.M.R. (DMSO) 7.06 d [2] $J = 8.4$ Hz ($2 \times C_5-H$), 7.6-7.3 complex [4] (aromatic H), 3.85s, 3.81s [12] ($4 \times ArOCH_3$); ν_{max} 1663 broad, 1600, 1514, 1145; λ_{max} 233, 287, 325 λ_{max} lit⁴ 230, 284, 322; mass m/e 330 (M^+) [6%], 165 [100%], metastable 82.5.

This reaction was repeated in the absence of the amine, but otherwise under the same conditions. Only starting ketone (33c) was recovered (76%). There was no trace of any veratril.

Condensation of 4-benzyloxy-3-methoxyphenyl-3,4-methylenedioxy-benzyl ketone (33b) with aminoacetaldehyde dimethyl acetal

The ketone (33b) (2.1g) and the acetal (2.0g) with P.T.S.A. (10mg) was heated under reflux in a Dean and Stark apparatus. After 24hr. the solvent was removed to give a red gum which crystallised over acetone to give the amide (38) (78mg) as white needles, m.p. 149° , N.M.R. ($CDCl_3$) 7.6-6.85 complex [8] (aromatic H), 5.23 s [2] ($PhCH_2O$), 4.48 t [1] $J = 6$ Hz ($CH_2-CH(OMe)_2$), 3.94 s [3] ($ArOCH_3$), 3.59 t [2] $J = 6$ Hz ($CH_2CH(OMe)_2$), 3.44 s [6] ($CH_2CH(OMe)_2$); ν_{max} 3280, 1627, 1225, 1110; λ_{max} (ϵ) 295 (4,700), 254 sh (8,700), 248 sh (6,900), 265 sh (9,000), 260 (9,400); mass m/e 345 (M^+) [7%], 241 [3%], 91 [91%], 75 [100%]. (Found: 345.1574 $C_{19}H_{23}NO_5$ requires 345.1576). The

remainder of the material, ν_{\max} 1638, was a pale red oil considered to be the crude Schiffs base (37) (2.2g) was reduced with NaBH_4 in EtOH in the normal manner to afford $\text{N}-[\alpha-(4\text{-benzyloxy-3-methoxy-benzyl})-3',4'\text{-methylenedioxybenzyl}]\text{aminoacetaldehydedimethyl acetal}$ (58) (1.7g., 55%) as a white solid m.p; 167-8°. N.M.R. (D.M.S.O.) 7.55-6.6 complex [11] (aromatic H), 5.97 s [2] (OCH_2O), 5.04 s [2] (PhCH_2O), 4.33 t [1] $J=5.5$ Hz ($\text{CH}_2\text{CH}(\text{OMe})_2$), 3.7 s [3] (ArOCH_3), 3.14 s [6] ($\text{CH}_2\text{CH}(\text{OMe})_2$), 3.75-3.6 m [1] (ArCHCH_2), 2.8-2.3 complex [4] ($\text{CH}_2\text{-CH}(\text{OMe})_2$ and ArCH_2CH); ν_{\max} 3310, 1510, 1140, 925, 740, 700; λ_{\max} (ϵ) 287 (5,670), mass m/e 464 (M^+-1) [2%], 361 [8%], 330 [100%], 75 [100%], 91 [94%]. Found: 464.2063, $\text{C}_{27}\text{H}_{30}\text{NO}_6$ (M^+-1) requires 464.2073.

$\text{N}-[\alpha-(4\text{-hydroxy-3-methoxybenzyl})-3',4'\text{-methylenedioxybenzyl}]\text{aminoacetaldehydedimethyl acetal}$ (58b) was obtained (115mg 62%) from its benzyl ether (58a) (230mg) by hydrogenolysis in 95% EtOH (100ml) over 10% Pd/C at R.T. and 45 lb/sq in of H_2 for 3hr. The product was obtained as a white crystalline solid from C_6H_6 , m.p. 113-5°, N.M.R. (CDCl_3) 6.85-6.65 complex [6] (aromatic H), 5.89 s [2] ($\text{O-CH}_2\text{-O}$), 4.6 m [1] (Ar-CH-NH), 4.35 t [1] $J=5.5$ Hz ($\text{CH}_2\text{-CH}(\text{OMe})_2$), 3.78 s [3] (ArOCH_3), 3.7 m [2] ($\text{Ar-CH}_2\text{-CH}$), 3.24 s [6] ($\text{CH}_2\text{-CH}(\text{OMe})_2$), 3.2-2.8 broad [1] (OH , NH , removed by D_2O), 2.55 d [2] $J=5.5$ Hz ($\text{CH}_2\text{-CH}(\text{OMe})_2$), ν_{\max} 3500, 3300, 1513, 1245, 1078. (Found: C, 63.3; H, 6.3; N, 3.5. $\text{C}_{20}\text{H}_{25}\text{NO}_6$ requires C, 64.0; H, 6.7; N, 3.7%).

Cyclisation of the acetal (58a).

The acetal (58a) (1.0g) in 6N ethanolic HCl (50ml) was stood at R.T. for 2hr., then heated under reflux for a further 2hr. After removal of the EtOH under reduced pressure, the remaining acid soln. extracted with ether (2 x 30ml). The clear, yellow acid soln. was basified with NaHCO_3 and extracted into CHCl_3 (4 x 30ml); the combined organic extracts were washed (H_2O), dried (MgSO_4) and evaporated to give an off-white solid which crystallised from MeOH to give the pavine (59) (264mg, 39%) as hard white crystals m.p. $257-8^\circ$, N.M.R. (T.F.A.) 7.85 broad s [2] (NH_2^+), 6.85 s [1], 6.75 s [2] and 6.57 s [1] (4 x aromatic H). 5.94 and 5.90 two singlets [2] (OCH_2O), 5.2-5.0 broad unresolved m [2] (2 x methine H), 3.96 s [3] (ArOCH_3), 3.74 broadened doublet [2] $J=17.2$ Hz and 3.10 d [2] $J=17.2$ Hz (4 x benzylic CH_2 , for further assignment see p132); ν_{max} 3280 sharp, 3100-2400 broad, 1605, 1480, 1230, 1118, 920, 855; λ_{max} (ϵ) 295 (7,340); λ_{max} (ϵ) (EtOH/NaOH) 300 (7,600); mass m/e 311 (M^+) [80%], 176 [91%], 178 [100%]. (Found: C, 69.1; H, 5.6; N, 4.7. $\text{C}_{18}\text{H}_{17}\text{NO}_4$ requires: C, 69.4; H, 5.5; N, 4.5%).

Chromatography over alumina of the residues ($\text{C}_6\text{H}_6/\text{CHCl}_3$) afforded an impure solid m.p. $205-10^\circ$; mass m/e 311 (M^+) [82%], 282 [75%], 176 [100%], 174 [20%]; ν_{max} 3280w, 1496, 1221; λ_{max} 299. This was considered to be isopavine (62) contaminated with pavine (59).

Condensation of 3,4-dimethoxybenzyl 3,4-dimethoxyphenyl ketone (33e)
with aminoacetaldehydedimethyl acetal

Under identical conditions to those used for the ketone (33b) the only solid product obtained by recrystallisation of the gummy product was veratril (36) (7%) m.p. $227-9^{\circ}$ lit⁴ 229° .

N-Methyl-N-(α -cyano-3-methoxy-4-benzyloxybenzyl)aminoacetaldehyde
diethylacetal (43).

N-methylaminoacetaldehydediethylacetal hydrochloride (17g) in water (10ml) was stirred with sodium cyanide (8g). Vanillin O-Benzyl ether () (17.5g) in MeOH (150ml) was added over 2hr. and the reaction mixture stirred at 35° for 24hr. The reddish solution was diluted with water (500ml) and extracted into ether (4 x 100ml). The combined ether extracts were washed with water, dried (MgSO_4) and removed to give the aminonitrile (43) (24g, 87%) as a reddish oil; N.M.R. (CDCl_3) 7.5-6.75 complex [8] (Aromatic H), 5.10 s [2] ($\text{Ph}-\text{CH}_2-\text{O}$), 5.01 s [1] ($\text{CH}-\text{CN}$), 4.59 t [1] $J=5.3$ Hz ($\text{CH}_2-\text{CH}-(\text{OEt})_2$), 3.85 s [3] ($\text{Ar}-\text{OCH}_3$), 3.5 two quartets [4] $J=7.0$ Hz (OCH_2CH_3)₂, 2.65 d [2] $J=5.3$ Hz ($\text{CH}_2-\text{CH}(\text{OEt})_2$), 2.30 s [3] ($\text{N}-\text{CH}_3$), 1.17 and 1.14 two triplets [6] $J=7.0$ Hz (OCH_2CH_3)₂; ν_{max} liquid film 2215, 1598, 1510 strong, 1270, 1145, 1065, 1030; λ_{max} (ϵ) 310 sh (1260), 281 (4400), 234 (11,400); mass m/e 393 (M^+) [1%], 308 [3.6%], 271 [3.6%], 242 [5.7%], 103 [100%], 91 [100%]. (Found: M^+ (398.2207 $\text{C}_{23}\text{H}_{30}\text{H}_2\text{O}_4$ requires: 398.2206).

N-Methyl-N-(α -cyano-3-benzyloxy-4-methoxybenzyl)aminoacetaldehyde diethylacetal (44) was prepared similarly (90%). N.M.R. (CDCl_3), 7.5-6.75 complex [8] (Aromatic H), 3.16 s [2] ($\text{Ph}-\text{CH}_2-\text{O}$), 5.02 s [1] ($\text{CH}-\text{CN}$), 4.59 t [1] $J=5.2$ Hz ($\text{CH}_2-\text{CH}-(\text{OEt})_2$), 3.89 s [3] ($\text{Ar}-\text{OCH}_3$), 3.55 two quartets [4] $J=7.0$ Hz (OCH_2CH_3)₂, 2.69 d [2] $J=5.2$ Hz ($\text{CH}_2-\text{CH}(\text{Et})_2$) 2.28 s [3] ($\text{N}-\text{CH}_3$), 1.20 and 1.17 two triplets [6] $J=7.0$ Hz (OCH_2CH_3)₂; ν_{max} liquid film 2220, 1598, 1510 strong, 1265, 1140, 1065, 1028; λ_{max} (ϵ) 310 sh (1310), 281 (4140); mass m/e 398 (M^+) [2%], 91 [100%]; (Found: M^+ (398.2207) $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4$ requires 398.2206).

By an analogous procedure using veratraldehyde (1.2g) aminoacetaldehydedimethyl acetal hydrochloride (1.6g) and NaCN (0.8g), N-(α -cyano-3,4-dimethoxybenzyl)aminoacetaldehyde dimethyl acetal (45) was obtained as a pale lemon oil (1.87g, 92%), N.M.R. (CDCl_3) 7.11 d [1] $J=8$ Hz and 6.88 d [1] $J=8$ Hz (C_5-H and C_6-H), 7.08 s [1] (C_2-H), 4.83 s [1] ($\text{Ar}-\text{CH}-\text{CN}$), 4.50 t [1] $J=5$ Hz ($\text{CH}_2-\text{CH}(\text{OMe})_2$), 3.90 s [6] (2 x $\text{Ar}-\text{OCH}_3$), 3.40 s [6] ($\text{CH}_2-\text{CH}(\text{OMe})_2$), 2.89 d [2] $J=5.0$ Hz ($\text{CH}_2-\text{CH}(\text{OMe})_2$), 2.0 broad s [1] ($>\text{NH}$, removed by D_2O); ν_{max} 3300, 2220 weak, 1594, 1513, 1265, 1150; mass m/e 253 (M^+-HCN) [100%]. (Found: M^+-HCN 253.1300 $\text{C}_{13}\text{H}_{19}\text{NO}_4$ requires 253.1314).

Reaction of (45) with Benzyl chloride in the presence of base

The aminonitrile (45) (300mg), Na_2CO_3 (140mg) and benzyl chloride were heated under reflux in acetone for 3hr. After removal of the solvent under reduced pressure, the residue was digested in water and extracted into CHCl_3 (3 x 10ml). Removal

of the dried (MgSO_4) CHCl_3 afforded an oil (208mg) which solidified on standing. mass m/e 253 (M^+); ν_{max} 1647. The sample was identical by I.R. and T.L.C. with the authentic schiffs base (46) prepared from veratraldehyde and aminoacetal heated under reflux in benzene.

N-Methyl-N-[α -(3,4-methylenedioxybenzyl)-3'-methoxy-4'-benzyloxy-benzyl] aminoacetaldehyde diethylacetal (39).

The aminonitrile (43) (16g) in dry DMF (100ml) under N_2 was stirred at 50° overnight with NaH (1.0g). The blood red anion was cooled to room temperature and 3,4-methylenedioxybenzyl chloride (8g) in DMF (25ml) was added dropwise over 6hr. The reaction was stirred for a further 24hr. and the excess NaH destroyed with MeOH. The solvent was removed under lmm pressure, at 90° over 6hr and the crude enamine () was reduced with aqueous ethanolic sodium borohydride for 4hr on a steam bath. After leaving to stand overnight the solvent was removed, water added (250ml), and the mixture extracted with ether (3 x 100ml). The combined ether extracts were washed with 2N NaOH (2 x 50ml) and water (2 x 100ml), dried (MgSO_4) and evaporated to leave a mixture of the required (39) contaminated with some unalkylated (47). Chromatography over alumina and elution with petrol (40-60)/benzene gave a pure sample of (39). N.M.R. (CDCl_3), 7.5-6.65 complex [11] (Aromatic H), 5.92 s [2] ($-\text{O}-\text{CH}_2-\text{O}-$), 4.98 s [2] ($\text{Ph}-\text{CH}_2-\text{O}-$), 4.51 t [1] $J=5.2$ Hz ($-\text{CH}-\text{CH}_2-\text{N}$), 3.8-2.7 complex [7] $(\text{OCH}_2\text{CH}_3)_2$ plus ($\text{Ar}-\text{CH}_2-\text{CH}$) 3.80 s [3] ($\text{Ar}-\text{OCH}_3$), 2.58 and 2.51 two doublets [2] $J=5.2$ Hz ($-\text{CH}-\text{CH}_2-\text{N}$), 2.35 s [3] ($\text{N}-\text{CH}_3$), 1.15 t [6] $J=7.1$ Hz $(\text{OCH}_2\text{CH}_3)_2$; mass m/e 507 (M^+) [1.8%], 372 [70%], 270 [51%], 242 [100%], 227 [100%].

Further chromatography over alumina and elution with benzene gave (47) as an oil. N.M.R. (CDCl_3) 7.5-6.5 complex [8] (Aromatic H), 5.14 s [2] ($\text{Ph}-\text{CH}_2-\text{O}-$), 4.64 t [1] $J=5.2$ Hz ($\text{CH}-\text{CH}_2-\text{N}$), 3.88 s [3] ($\text{Ar}-\text{OCH}_3$), 3.15 s [2] ($\text{Ar}-\text{CH}_2-\text{N}$), 2.57 two quartets [4] $J=7.1$ Hz (OCH_2CH_3)₂, 2.56 d [2] $J=5.2$ Hz ($\text{CH}-\text{CH}_2-\text{N}$), 2.30 s [3] ($\text{N}-\text{CH}_3$), 1.20 t [6] $J=7.2$ Hz (OCH_2CH_3)₂; mass m/e 373 (M^+) [5%], 328 [6%], 270 [12%], 227 [100%].

The uncharacterised crude enamine (41) (1.0g) was stirred in 6N HCl (50ml) for 18hr. and extracted into CHCl_3 (3 x 30ml), washed (H_2O) and dried (MgSO_4). Evaporation of the solvent afforded, a gum which crystallised under ether. Recrystallisation from MeOH afforded white needles (200mg), m.p. $98-9^\circ$ which showed the same N.M.R. and I.R. spectra as 4-benzyloxy-3-methoxyphenyl 3,4-methylenedioxybenzyl ketone (33b) prepared from the aminonitrile (32a) (p159).

Experimentally it was found best to subject the mixture of (39) and (47) to the cyclisation conditions and to purify the final mixture by column chromatography.

N-Methyl-N-[α -(3,4-methylenedioxybenzyl)-3'-benzyloxy-4'-methoxybenzyl]aminoacetaldehyde diethylacetal (40).

This was obtained, together with (53) by an analogous method to the above procedure. The acetal (40) was obtained as an oil. N.M.R. (CDCl_3) 7.55-6.3 complex [11] (Aromatic H), 5.84 s [2] ($-\text{O}-\text{CH}_2-\text{O}-$), 5.13 s [2] ($\text{Ph}-\text{CH}_2-\text{O}-$), 4.51 t* [1] $J=5.2$ Hz ($\text{CH}-\text{CH}_2-\text{N}$), 3.8-2.65 complex [7] (OCH_2CH_3)₂ plus (ArCH_2-CH), 3.85 s [3] ($\text{Ar}-\text{OCH}_3$),

2.56 and 2.51 two doublets [2] $J=5.2$ Hz ($\text{CH}-\text{CH}_2-\text{N}$), 2.25 s [3] ($\text{N}-\text{CH}_3$, 1.18 t [6] $J=7.1$ Hz (OCH_2CH_3)₂); ν_{max} (CHCl_3 solution) 1506, 1491, 1446, 1253; mass m/e 507 (M^+) [1%], 372 [86%], 270 [45%], 242 [98%], 227 [100%].

The amine (53) was eluted from the alumina column with benzene as an oil. N.M.R. (CDCl_3) 7.5-6.5 complex [8] (Aromatic-H), 5.14 s [2] ($\text{Ph}-\text{CH}_2-\text{O}$), 4.62 t [1] $J=5.2$ Hz ($\text{CH}-\text{CH}_2-\text{N}$), 3.84 s [3] ($\text{Ar}-\text{O}-\text{CH}_3$), 3.50 s [2] ($\text{Ar}-\text{CH}_2-\text{N}$), 3.57 two quartets [4] $J=7$ Hz (OCH_2CH_3)₂, 2.55 d [2], $J=5.2$ Hz ($\text{CH}-\text{CH}_2-\text{N}$), 2.25 s [3] ($\text{N}-\text{CH}_3$), 1.18 t [6] $J=7$ Hz (OCH_2CH_3)₂; ν_{max} (CHCl_3 solution) 1508, 1255, 1056, 1023; mass m/e 373 (M^+) [4.4%], 328 [4.4%], 270 [18.5%], 227 [100%].

The uncharacterised crude enamine (42) (1.0g) was stirred in 6N HCl (50ml) for 18hr. and extracted into CHCl_3 (3 x 30ml), washed (H_2O) and dried (MgSO_4). Evaporation of the solvent afforded a white solid, m.p. $144-5^\circ$ (EtOH) which showed the same N.M.R. and I.R. spectra as 3-benzyloxy-4-methoxyphenyl 3,4-methylenedioxy benzyl ketone (33c) prepared from the aminonitrile (32b) (p160).

Cyclisation to the isopavine (69) and the pavine (51). The mixture of alkylated and unalkylated benzylamines (39) and (47) was cyclised without separation by standing overnight in 6N HCl. The solution was then heated on a steam bath for 6hr, cooled, diluted with water and extracted into ether (2 x 100ml). The aqueous solution was basified with sodium bicarbonate and extracted into CHCl_3 (4 x 100ml). The combined CHCl_3 extracts were washed with NaHCO_3 , water and dried (MgSO_4). Evaporation of the CHCl_3 layer afforded a yellow solid. Chromatography on silica preparative plates, eluting with CHCl_3 afforded the pavine (51) (9% based on starting aldehyde ()) Crystallisation from MeOH gave a white solid

m.p. 240-1°, N.M.R. (CDCl_3), 6.59 s [2] (Ar-H), 6.48 s [1] (Ar-H), 6.44 s [1] (Ar-H), 5.94 broad s [1] (OH, removed by D_2O), 5.79, 5.85 two doublets $J=1.4$ Hz ($\text{OCH}_2\text{-O}$), 3.83 s [3] (Ar-OCH_3), 2.52 s [3] (N-CH_3), 4.10-4.20 complex [6] (aliphatic H); N.M.R. (CD_3SOCD_3), 6.75 s [1] (Ar-H), 6.72 s [1] (Ar-H), 6.51 s [1] (Ar-H), 6.39 s [1] (Ar-H), 5.92, 5.87 two s broad [2] ($\text{OCH}_2\text{-O}$), 3.75 s [3] (Ar-OCH_3), 2.38 s [3] (N-CH_3), 4.0-2.2 complex [6] (aliphatic H); ν_{max} (CHCl_3) 3400-3200, 1505, 1487, 1253; λ_{max} (ζ) 293 (9000) on the addition of NaOH λ_{max} 302; λ_{max} (hexane) resolved into 278, 284, 289, 302, 294; mass m/e 326 ($\text{M}^+ + 1$) [11%], 325 (M^+) [69%], 324 ($\text{M}^+ - 1$) [46.5 %], 282 [5%], 190 [99%], 188 [100%]. (Found: C, 70.1; H, 5.9; N, 4.3. $\text{C}_{19}\text{H}_{19}\text{NO}_4$ requires C, 70.1; H, 5.9; N, 4.3%).

The slowest fractions from the silica plate were extracted into MeOH by soxhlet and plated on alumina. Elution with CHCl_3 afforded the isopavine (6g) (8% based on starting aldehyde) m.p. 186-7 (EtOH). N.M.R. (CDCl_3) 6.50 s [1] (Ar-H), 6.63 s [1] (Ar-H), 6.75 s [2] (2x Ar-H), 5.86 and 5.82 two doublets [2] $J=1.5$ Hz ($\text{OCH}_2\text{-O}$), 5.30-5.0 broad s [1] (-OH, removed by D_2O), 3.85 s [3] (Ar-OCH_3), 3.85-2.30 complex [6] (aliphatic H); N.M.R. (CD_3SOCD_3), 6.39 s [1] (Ar-H), 6.81 s [1] (Ar-H), 6.72 s [1] (Ar-H), 6.58 s [1] (Ar-H), 5.90 broad s [2] ($\text{O-CH}_2\text{-O}$), 6.2-5.5 broad [1] (OH, removed by D_2O), 3.76 s [3] (Ar-OCH_3), 2.39 s [3] (N-CH_3), 3.8-2.3 complex [6] (aliphatic H); PART N.M.R. (CD_3COCD_3), 6.90 s [1] (Ar-H), 6.76 s [1] (Ar-H), 6.68 s [1] (Ar-H), 6.46 s [1] (Ar-H), 5.86 and 5.83 two doublets [2] $J=1.5$ Hz

($\text{O}-\text{CH}_2-\text{O}$); ν_{max} (CHCl_3 solution) 3450 sharp 3300-3000, 1602, 1505, 1485, 1370 broad, 1260, 1220 broad, 1102, 1038, 934, 860; λ_{max} (ζ) 294 (7,000), 230 sh (10,000), on the addition of NaOH λ_{max} 302; Peak resolution in hexane not as complete as with pavines(51) and (54); mass m/e 325 (M^+) [27%], 324 (M^+-1) [26%], 282 [22%], 190 [100%], 188 [4%], metastables 244.5, 213.5, 214, 215. The methiodide salt formed from acetone with a mole of solvent m.p. $214-18^\circ$ (Found: C, 53.3; H, 5.1; N, 2.9; $\text{C}_{20}\text{H}_{22}\text{NO}_4\text{ICH}_3\text{COCH}_3$ requires C, 52.6; H, 5.4; N, 2.7%).

Cyclisation to the Isopavine (6h) and the Pavine (54). The mixture of (40) and (53) was cyclised in an analogous manner to yield a solid containing the required isopavine (6h) and the pavine (54). The mixture was dissolved in CHCl_3 and stirred with SiO_2 overnight. The silica was filtered and washed with hot CHCl_3 , and the combined CHCl_3 washings were evaporated to afford a gum which crystallised from acetone as the pavine (54) (15% on starting aldehyde) with 1 mole of solvent of crystallisation. (Found: C, 69.3; H, 6.3; N, 3.9; $\text{C}_{19}\text{H}_{19}\text{NO}_4\text{CH}_3\text{COCH}_3$ requires: C, 68.9; H, 6.6; N, 3.7%). The mole of acetone was removed under vacuum at 110° , to afford crystalline pavine m.p. $206-7^\circ$ N.M.R. (CDCl_3) 6.67 s [1] (Ar-H), 6.60 s [1] (Ar-H) 6.44 s [2] (2xAr-H), 5.87 and 5.82 two doublets [2] $J=1.5$ Hz (OCH_2-O), 5.4-5.1 broad s (OH, removed by D_2O), 3.77 s [3] (Ar- OCH_3), 2.53 s [3] (N- CH_3), 4.0-2.3 complex [6] (aliphatic H); N.M.R. (CD_3SOCD_3), 6.75 s [1] (Ar-H), 6.58 s [1], (Ar-H), 6.51 s [2] (2xAr-H), 5.92, 5.88 two broad s [2] (OCH_2-O), 3.69 s [3] (Ar- OCH_3), 2.39 s [3]

$(N-CH_3)$, 3.95-2.2 complex [6] (Aliphatic H); ν_{max} 2700 broad, 1603, 1527, 1490, 1241, 1230, 1109, 1027; λ_{max} (ζ) 293 (9300), 225 sh (13,000), on the addition of NaOH λ_{max} (hexane) resolved into 279, 285, 290, 303; mass m/e 325 (M^+) [65%], 224 (M^+-1) [43%], 282 [4%], 188 [100%], 190 [76%]. Extraction of the SiO_2 with hot MeOH and subsequent plating on alumina afforded the isopavine (62) (9% based on starting aldehyde. Recrystallisation from EtOH afforded white crystals m.p. 215-16°, N.M.R. ($CDCl_3$), 6.70 s broad [2] (2xAr-H), 6.62 s [1] (Ar-H), 6.46 s [1] (Ar-H), 7.2-6.8 broad [1] (OH , removed by D_2O), 5.85 and 5.80 two unresolved doublets [2] $J=1$ Hz ($O-CH_2-O$), 3.80 s [3] (Ar- OCH_3), 2.44 s [3] ($N-CH_3$), 3.7-2.2 complex [6] (aliphatic H); N.M.R. (CD_3SOCD_3), 6.83 s [1] (Ar-H), 6.78 s [1] (Ar-H), 6.72 s [1] (Ar-H), 6.53 s [1] (Ar-H), 6.1-5.7 broad [1] (OH , removed by D_2O), 5.91 and 5.86 two doublets [2] $J=1$ Hz (OCH_2O), 3.74 s [3] (Ar- OCH_3), 2.31 s [3] ($N-CH_3$), 3.8-2.2 complex [6] (aliphatic H); PART N.M.R. (CD_3COCD_3) 6.88 s [1] (Ar-H), 6.79 s [1] (Ar-H), 6.70 s [1] (Ar-H), 6.48 s [1] (Ar-H), 5.88 and 5.84 two broad s [2] ($O-CH_2-O$). ν_{max} ($CHCl_3$ solution), 3450, sharp 3300-3000, 2300, 1602, 1500 strong, 1485 strong, 1368 broad, 1260, 1220 broad, 1102, 1038, 933, 868; λ_{max} 294 (8000), 230 sh (12,700), on the addition of NaOH λ_{max} 304; Peak resolution in hexane not as complete as with pavines (51) and (54); mass m/e 325 (M^+) [36.6%], 324 (M^+-1) [34.6%], 282 [38.5%], 190 [100%], 188 [0.9%], metastables 244.5, 213.5, 214, 215. (Found: C, 69.8; H, 6.05; N, 4.2; $C_{19}H_{19}NO_4$ requires: C, 70.1; H, 5.9; N, 4.3%).

Hofmann Degradation of (6h) to (66). The methiodide of (6h)

m.p. 245° (120mg) was heated on a steam bath for 6hr. under N_2 with MeOH (10ml) and KOH pellets (4g). The resulting red solution was evaporated to dryness, water (5ml) added and the solution acidified with 6N HCl, then basified with $NaHCO_3$. Extraction into ether and concentration of the ether phase afforded a pale yellow solid (90mg); mass m/e 339 (M^+) [7%], 281 [100%] metastable 232.7. Recrystallisation from EtOH afforded a white crystalline solid m.p. 184° , N.M.R. (CD_3SOCD_3), 6.95-6.68 complex [6] (4 x Aromatic H, plus 2 x olefinic H), 6.02 and 5.98 2 broad s [2] ($O-CH_2-O$), 4.12 t [1] $J=8$ Hz ($N-CH_2-CH$); 3.80 s [3] ($Ar-OCH_3$), 2.07 d [2] $J=8$ Hz ($N-CH_2-CH$), 2.01 s [3] ($N-(CH_3)_2$) λ_{max} ($CHCl_3$ solution) 3550 sharp, 3300 broad, 2900, 1595, 1485, 1267, 1040; λ_{max} (ϵ) 242 (17,400), 320 (10,440), on addition of NaOH λ_{max} 323, 260 sh mass m/e 339 (M^+) [9%], 281 [100%] metastable 232.7. (Found: C, 70.5; H, 6.2; N, 4.1. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 3.9%).

Hofmann Degradation of (6g) to (67). The methiodide of (6g)

was degraded to (12a) in an analogous manner to give a yellow solid, melting over $152-158^{\circ}$. This substance, which could not be further purified, contained a small amount of the alternative methine base (by N.M.R.). m/e 339 (M^+) [8%], 281 [100%] metastable 232.7; ν_{max} ($CHCl_3$ solution) 3550 sharp, 3300 broad, 1513, 1491, 1267, 1045, 945, 876; N.M.R. ($CDCl_3$) 6.9-6.5 complex [6] (Aromatic H plus olefinic H), 5.90 and 5.86 two doublets [2] $J=1.5$ Hz ($O-CH_2-O$), 4.7 broad [1] ($-OH$, removed by D_2O), 3.96 t [1] $J=8$ Hz ($N-CH_2-CH$) 3.84 s [3] ($Ar-OCH_3$), 2.6 d [2] $J=8$ Hz

(N-CH₂-CH), 2.1 s [3](N-(CH₃)₂) λ_{\max} (EtOH) 300, 320, 235 (sh).
 λ_{\max} (EtOH/NaOH) 300, 350, 260 (sh). (Found: C, 70.2; H, 6.2; N, 3.9. C₃₀H₂₉NO₄ requires C, 70.8; H, 6.2; N, 3.9%).

(±)-Reframine Methiodide. The isopavine (6g) (20mg) was methylated with an ethereal diazomethane solution for 20hr. The solution was evaporated, the residue dissolved in 2N H₂SO₄ and the solution basified with NaOH and extracted with ether. The ether solution of the non-phenolic base was treated with methyl iodide, and the precipitated product crystallised from methanol (12mg) m.p. 263-5°. A mixed m.p. with reframine methiodide m.p. 263-4°, melted at 263-265°. The I.R. spectrum of the product was identical with that of reframine methiodide.

The same treatment of isopavine (1f) afforded a white crystalline methiodide m.p. 262-4°, which when mixed with reframine methiodide melted at 262-4°.

The Pavine Methiodide. The pavines (51) and (54) were each methylated as described above and the methiodide salts of the products had m.p. 272-4°, undepressed upon admixture.

Pseudocyanide. A mixture of the alkylated and unalkylated acetals (40) and (53) (1g) was sealed under N₂ with concentrated HCl (1ml) and heated at 50° for 48 hr. After dilution with water (10ml) and washing with ether (2 x 10ml) the solution was basified with NaHCO₃ and extracted into CHCl₃ (3 x 15ml). The combined CHCl₃ extracts were washed with NaHCO₃ solution (2 x 5ml), brine (2 x 10ml) dried (MgSO₄) and evaporated to afford a yellow solid (270mg). The mass spectrum of these crude bases showed molecular ions corresponding with pavine, isopavine and unalkylated tetra hydroisoquinoline.

To the combined NaHCO_3 solution was added NaCN , followed by extraction into ether (3 x 20ml). The combined ether extracts were washed with brine, dried (MgSO_4) and concentrated to afford a pale yellow solid (20mg). λ_{max} 250sh, 289, 316. Addition of a drop of dilute HCl to the sample gave λ_{max} 253 strong, 315, 374. Mass m/e 325 (M^+-HCN), 190 (M^+-HCN and methylenedioxybenzyl), 217/218 ($\text{M}^+-\text{methylenedioxybenzyl}$). Reduction of the suspected pseudocyanide (72) with NaBH_4 in aqueous EtOH on a steam bath for 1hr. followed by workup for phenolic bases afforded an oil (10mg), λ_{max} 294, (typical tetrahydroisoquinoline); mass m/e 192 ($\text{M}^+-\text{methylene dioxybenzyl}$) [100%], 327 ($\text{M}^+)^{\frac{1}{2}}$ [3%].

Isolation of 1-benzyl-2-methyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (74).

The bases (400mg) from the acid catalysed cyclisation of the mixture of acetals (39) and (47) (p169) were dissolved in EtOH (40ml) and hydrogenated over 10% Pd/C under 30lb/sq in of H_2 . Removal of the catalyst and solvent afforded a yellow brown solid which was chromatographed by P.L.C. over silica. Successive elutions with $\text{CHCl}_3/\text{MeOH}$ 90/10, afforded at RF 0.15, a yellow band which was removed from the silica with cold MeOH . The product (100mg) was further chromatographed on silica with the same solvent system, removed by soxhlet with CHCl_3 and the solvent removed. Crystallisation of the product from acetone afforded pale yellow needles (28mg), 7% of bases) $m.p.$ $160-1^\circ$ lit⁵⁰ $157-8^\circ$, N.M.R. (CDCl_3) 7.3-7.0 broad [5] ($\text{C}_6\text{H}_5-\text{CH}_2$),

6.56 s [1] (C_5-H), 5.83 s [1] (C_7-H), 3.66 m [1] (C_1-H),
 3.44 s [3] ($ArOCH_3$), 2.48 s [3] ($N-CH_3$), 3.50-2.50 complex [6]
 ($3 \times CH_2$). This N.M.R. spectrum in agreement with that
 reported⁵⁰. ν_{max} (KBr disc) 3000 broad, 1510, 1273, 1112, 880,
 790, mass m/e 282 (M^+-1) [3%], 192 [100%], 177 [20%], 91 [14%].
 (Found: 282.1490. $C_{18}H_{20}NO_2$ (M^+-1) requires 282.1494)

Attempts to N-methylate the pavine (59)

Treatment of (59) (155mg) in EtOH (100ml) with formaldehyde
 (37%) (3ml) at R.T. for 48hr gave a clear soln which was stirred
 with $NaBH_4$ (4g) for 2hr. The mixture was then heated at steam
 bath temperature for a further 2hr and the solvent then removed
in vacuo. H_2O (20ml) was added to the residue which was extracted
 into $CHCl_3$ ($3 \times 20ml$). The bulked organic phase was washed (H_2O)
 dried ($MgSO_4$) and evaporated to give 151 mg of an off white solid.
 T.L.C. on silica eluted with $CHCl_3/MeOH$, 80/20 and subsequent iodine
 staining showed at R_F 0.8 the N-methyl pavine (51) with at R_F 0.72
 unreacted starting material (59). Mass m/e of mixture includes
 311 (M^+), 325 (M^+). I.R. includes 3280, 3100-2400.

The reaction above was repeated using 2 drops of glacial HAC
 to catalyse the condensation with $HCHO$. T.L.C. of the product
 compared with authentic samples of (51) and (59) showed the
 presence of unreacted (59).

Formation of the N-oxide (63) of pavine (51).

A soln of the pavine (51) (150mg) in MeOH (25ml) was stirred
 at R.T. for 48hr. with H_2O_2 (30%, 3ml) and the product collected
 by filtration (96mg, 61%) m.p. $248-52^\circ$, ν_{max} 3320, 1265 strong,
 1248 strong; mass m/e 341 (M^+) [4%], 325 [60%], 324 [56%],
 190 [96%], 188 [100%]; T.L.C. silica ($CHCl_3/MeOH$, 80/20).

Iodine stained, RF 0.4 of pavine (51) RF 0.82.

Treatment of the N-oxide (63) with SO₂.

To the N-oxide (63) 90mg was added liquid SO₂ (10ml), followed by N,N-dimethylacetamide (1ml). After 48hr at about -40°, excess SO₂ was removed, conc. HCl (1ml) was added and the mixture heated on a steam bath for 5min. Basification with NaHCO₃, followed by CHCl₃ extraction, yielded a solid product (61mg) which crystallised from MeOH m.p. 240°, T.L.C. comparison with authentic (51) confirmed regeneration of starting pavine.

Reaction of the pavine (51) with ethylchloroformate

A soln of (51) (150mg) in CHCl₃ (10ml) was stirred for 18hr with K₂CO₃ (80mg) and ethylchloroformate (2ml). Water (5ml) was added and the CHCl₃ layer separated, dried (MgSO₄) and evaporated to afford the dicarbethoxypavine (64) (185mg, 88%) m.p. 200-1°, N.M.R. (DMSO) 7.13 s [1], 6.89 s [1], 6.80 s [1], 6.52 s [1] (4 x aromatic H), 5.91 and 5.85 [2] singlets [2] (O-CH₂-O), 5.5-5.25 broad s [2] (2 x methine H),²² 4.16 q [2] J=7.5 Hz and 4.10 q [2] J=7.5 Hz (OCOCH₂CH₃ and N-COOCH₂CH₃), 3.76 s [3] (ArOCH₃), 3.3-2.5 complex [4] (2 x benzylic CH₂), 1.24 t [3] J=7.5 Hz and 1.19 t [3] J = 7.5 Hz (OCOCH₂CH₃ and NCOOCH₂CH₃); ν_{\max} 1757, 1690; λ_{\max} (EtOH) 290 (7200), 295 sh (6000), 280sh (5,600); λ_{\max} (EtOH/NaOH) same as above; mass m/e 455 (M⁺) [11%], 381 [6%], 246 [100%].

Alkali hydrolysis of dicarbethoxypavine (64)

A soln. of (64) (160mg) in EtOH (2ml) and NaOH (30%, 10ml) under N₂ was heated under reflux for 3hr. The EtOH was removed in vacuo and the caustic soln acidified with HCl then extracted into ether (4 x 50ml). The combined ether phase was extracted

with 2N HCl (3 x 10ml) followed by 2N NaOH (3 x 10ml), then H₂O. After drying (MgSO₄) the ether was removed to afford the starting material (64) (152mg) m.p. 199-200°. The same material was redissolved in EtOH (2ml) and NaOH soln (50%, 10ml) under N₂ and heated under reflux for 18hr. The same workup procedure as above afforded a pale yellow 2N HCl soln which was basified (NaHCO₃) and extracted into CHCl₃ to afford a white solid (57mg, 59%) m.p. 256-8° (MeOH), mixed m.p; with synthesised (59) 256-8°; ν_{\max} 3280, 3100-2400, 1605, 1480, 1230, 1118, 920, 856 superimposable on spectrum of (59). T.L.C. on silica (CHCl₃/MeOH, 80/20) followed by I₂ staining showed single spot at RF 0.7 (authentic sample of (59) RF 0.7. T.L.C. of product showed no spot at RF 0.8 corresponding with pavine (51). mass m/e 311 (M⁺) [78%], 176 [90%], 178 [100%].

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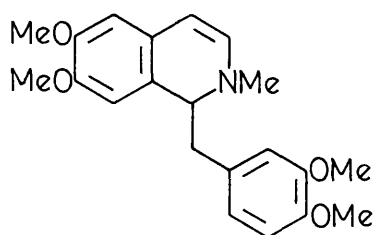
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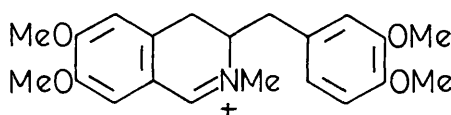
CHAPTER 3

CHAPTER 3 : INTRODUCTION1. Background

In 1963, it was reported¹ that when 2-methyl-1,2-dihydro-papaverine (1a) was treated with dilute acid at 100°, a high yield of the 2-methyl-3-benzyl-3,4-dihydroisoquinolinium salt (2) was formed. The mechanism of this conversion was of great

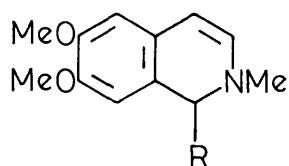


(1a)

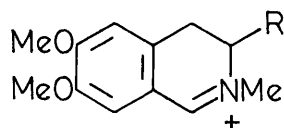


(2)

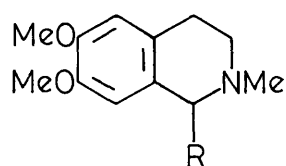
interest, being a 1,3 shift occurring with considerable ease. Movement of the $C=N^+$ bond into conjugation with the benzenoid aromatic system presumably provides the necessary energy gain to promote the migration. Knabe and Ruppenthal² studied potential migrating groups by subjecting a number of 1-substituted 1,2-dihydroisoquinolines (3) to the rearrangement conditions. They found that when R=benzyl, or alkoxy substituted benzyl, rearrangement occurred to give the 3-substituted 3,4-dihydroisoquinolinium salt (4), but when R=phenyl, phenylethyl, methyl or butyl, disproportionation to (5) and (6) was the only reaction detected.



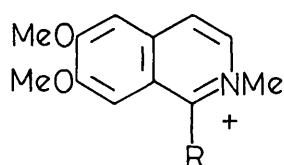
(3)



(4)

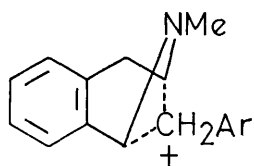


(5)



(6)

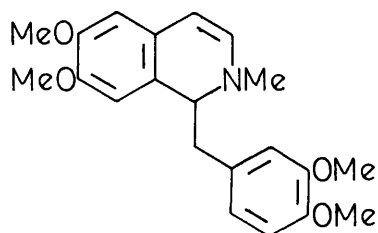
It was suggested by Dyke and Sainsbury³ that the rearrangement involves an intermediate of the type (7), but this mechanism, essentially intramolecular in nature, was quickly disproved by



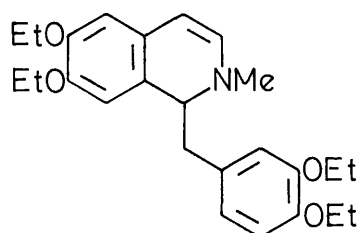
(7)

demonstration of the intermolecular character of the reaction as detected by a crossed migration experiment⁴. A mixture of

equimolar quantities of 2-methyl-1,2-dihydropapaverine (1a) and 2-methyl-1,2-dihydrobarbonine (8) was treated with dilute acid

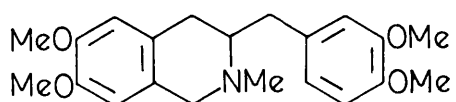


(1a)

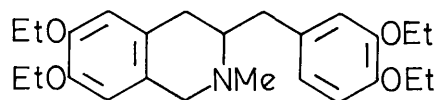


(8)

and the products examined, both as the ψ -cyanides and the 1,2,3,4-tetrahydroisoquinolines. The presence of the two symmetrically substituted products (9) and (10) was confirmed by T.L.C. and G.L.C. comparisons with authentic compounds,

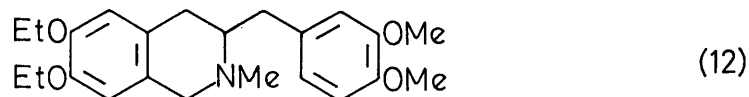
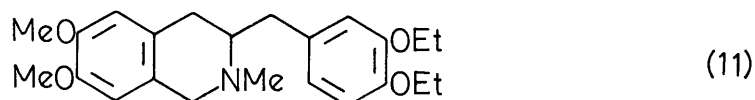


(9)



(10)

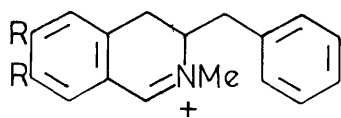
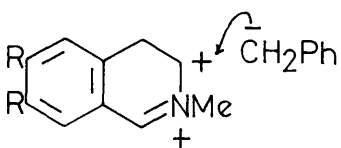
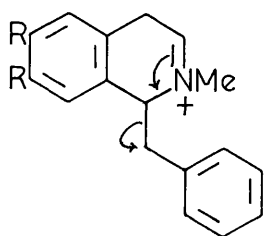
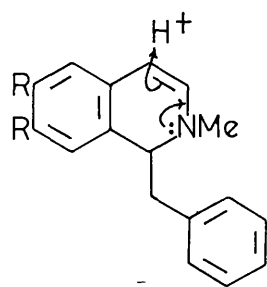
and the unsymmetrically substituted products (11) and (12) were also synthesised but could not be separately detected by the



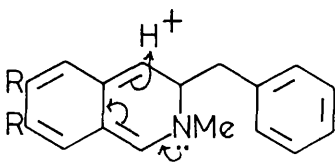
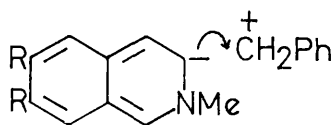
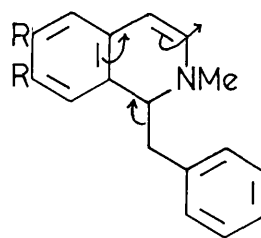
chromatographic techniques used. Examination of the products of the mixed migration revealed material with the same chromatographic properties as a mixture of authentic samples of (11) and (12), and the total products from this reaction were shown to be in the ratio (9):(10):(11) + (12) as 1:1:2, indicating an absolute intermolecularity for the migration.

In these laboratories^{5,6} the various competing reactions of 1-benzyl-2-methyl-1,2-dihydroisoquinoline and the effect of altering the strength and molar ratios of the acids used were investigated. Rearrangement was the predominant reaction under all of the conditions employed, with pavine formation occurring at higher temperatures and greater acid:base ratios.

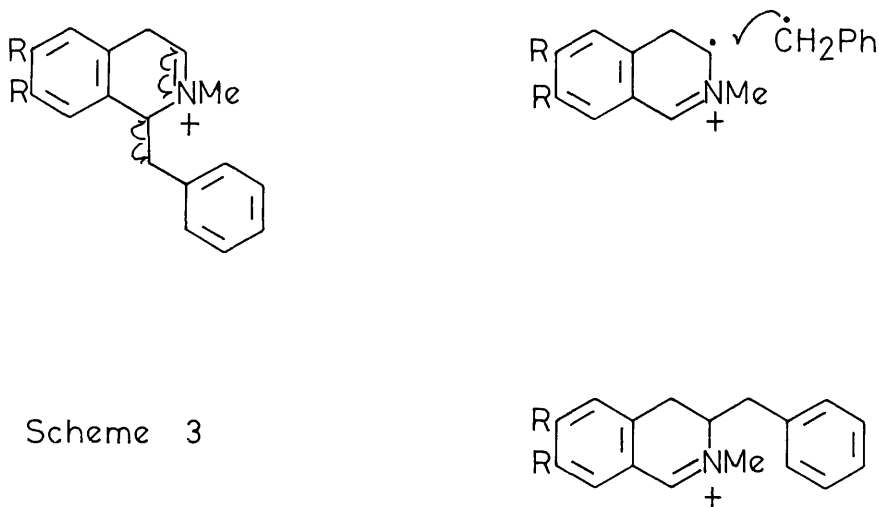
In 1970, Knabe and Powilleit⁷ published and discussed three possible mechanisms for the benzyl \rightarrow dihydroisoquinoline rearrangement; two of them were ionic, namely migration of the benzyl group as an anion (scheme 1), or as a cation (scheme 2), and one radical type (scheme 3). They argued that as the rearrangement was carried out in dilute acid at 100°, the



Scheme 1

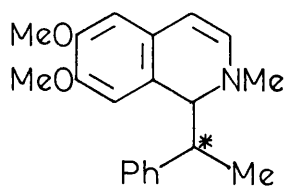


Scheme 2

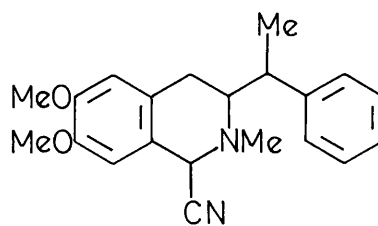


radical mechanism seemed highly improbable. Of the other routes, migration of the benzyl group as an anion was favoured over the cationic migration, which they suggested would require disruption of aromaticity in the carbocyclic ring.

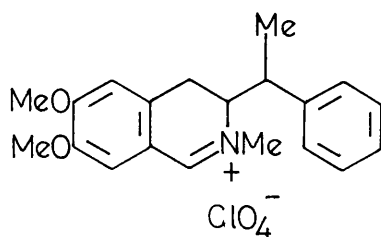
The rearrangement of an optically active sample of (13) has been reported⁷ to yield an optically inactive pseudocyanide (14). A re-examination of this reaction^{8,9} has revealed that the perchlorate (15) derived from (14) is optically active. This, it was considered, was support for the anionic mechanism over the cationic one. It was assumed⁹ that if the benzyl group becomes completely free during the migration the cationic form (16a) is sp² hybridised and can easily become planar such that optical



(13)

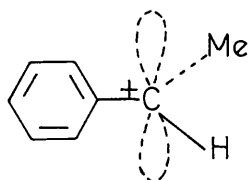


(14)

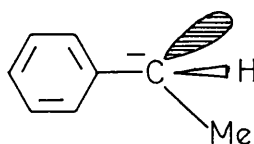


(15)

activity cannot be retained. If the anionic form (16b) is stabilised by solvation of its lone pair of electrons, before inversion occurs, it was considered that optical activity might



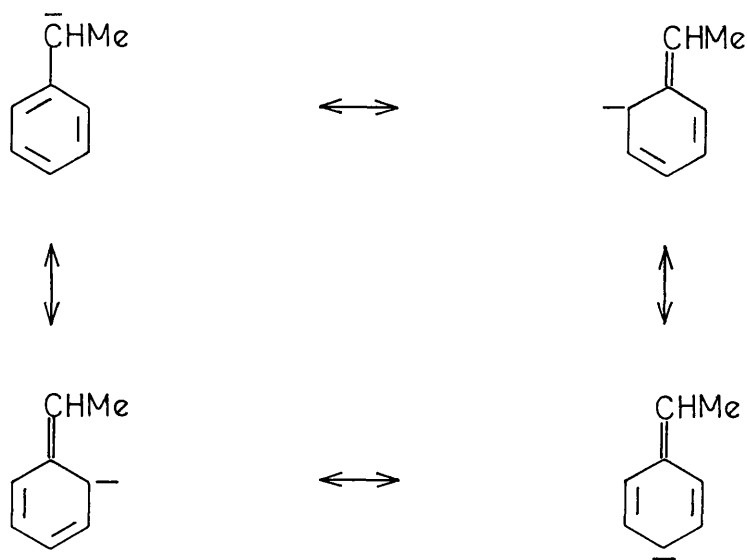
(16a)



(16b)

be retained. Further it was argued that stabilisation of the benzyl anion could, however, be achieved by charge delocalisation involving the aromatic π system (17), resulting in racemisation

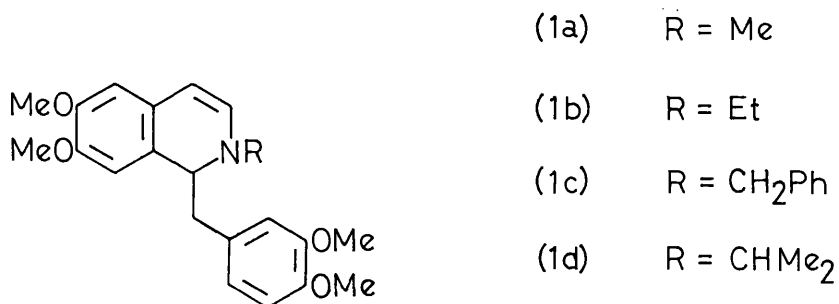
at the chiral centre.



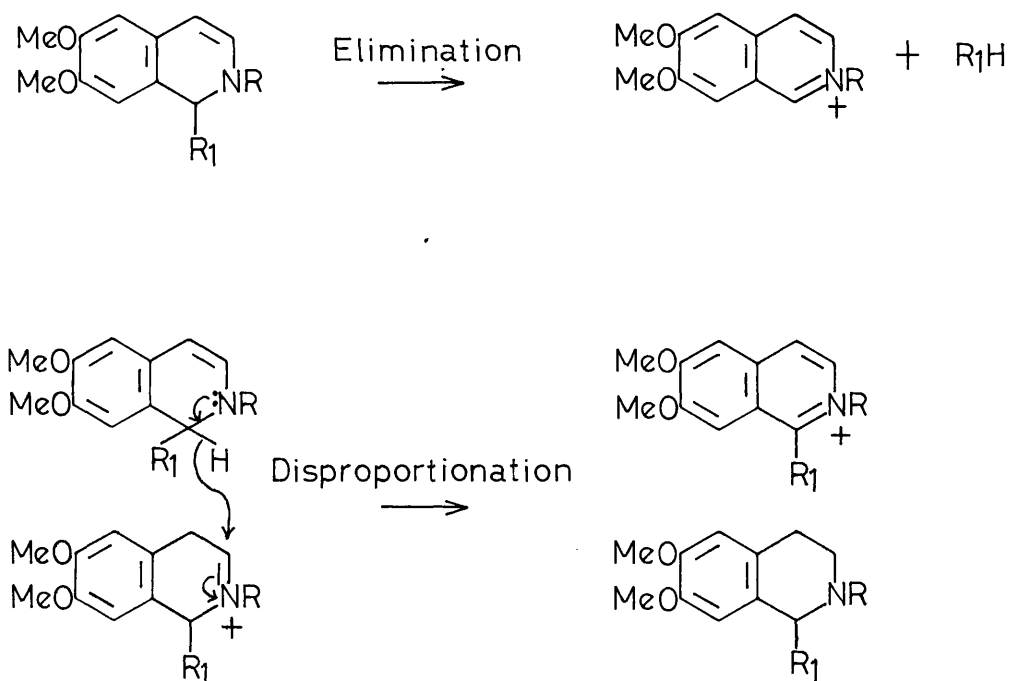
(17)

Having already demonstrated¹⁰ that an oxygen function at C₆ favours rearrangement, Knabe and Sierocks went on to study the effect of substituents in the benzyl ring¹¹, on the yield of rearrangement product. They concluded that electron donating substituents suppress rearrangement and electron withdrawing substituents promote elimination.

In a subsequent study by Knabe and Powilleit¹² an interesting effect was reported when the migration was carried out on 1,2-dihydropapaverine (1) with varying groups attached to the nitrogen atom (1a-d). Elimination and disproportionation



occurred (scheme 4), but whereas these side reactions gave similar yields in all cases, the yield of rearrangement product decreased with increased size of R.



Scheme 4 $R_1 = 3,4\text{-dimethoxybenzyl}$

Summarised below (a-e) are the factors known concerning the rearrangement, which Knabe et al⁸ appreciated should be taken into account in any satisfactory mechanism.

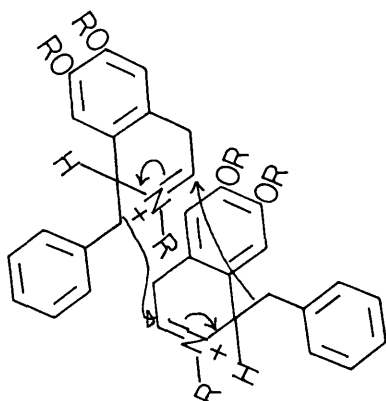
- (a) The reaction is intermolecular.
- (b) The rearrangement involves initial protonation of the enamine at C₄ to form a 1,4-dihydroisoquinolinium ion.
- (c) The yield of the rearrangement product, as compared with the yields of materials from the competing elimination and disproportionation reactions, depends strongly on the concentration of the enamine. (A decrease in enamine concentration results in a decrease in the yield of rearrangement product¹³).
- (d) The substituent effects discussed above, and the failure of groups such as aryl and alkyl to migrate, suggest that C₁^{δ+}-CH₂^{δ-}-Ar bond is polarised as indicated.
- (e) An increase in the size of the substituent on nitrogen results in a decrease in yield of the rearrangement product.

Knabe in collaboration with Dyke⁸ considered that the intermolecular character of the reaction could be interpreted in two ways.

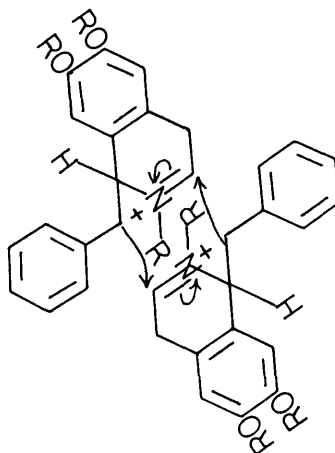
1. That the reaction involves the migration of a benzyl group, probably as an anion, to a second isoquinoline moiety which loses or has already lost its C₁ substituent.
2. A concerted bimolecular exchange reaction.

It was suggested⁸ that observation (e) seems to exclude the separation of the benzyl group as an ion, or radical, but that it is compatible with an exchange mechanism. Moreover the fact that the reaction takes place in an aqueous solution was considered

hardly compatible with the formation of free ions or radicals. Kinsman⁹ suggested that if ion separation were to occur, one would expect the elimination reaction to predominate under the conditions employed. In order to explain the high degree of intermolecularity, as well as retention of optical activity, it was proposed⁸ that migration occurs by the concerted bimolecular reaction pathway 2. Consequently two possible transition states (18) and (19) were postulated, in which the C_1 atom of one molecule lies opposite to the C_3 atom of the second molecule and vice versa. Both transition states allow for an exchange of benzyl groups and



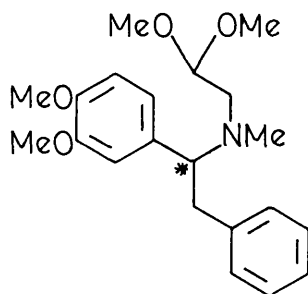
(18)



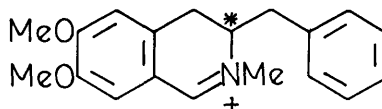
(19)

the movement of double bonds to occur in a cyclic and synchronous manner. In one postulate (18) both molecules of the 1,4-dihydroisoquinolinium ion, that make up the transition state must possess the same configuration at C_1 , whereas the alternative possibility (19) requires the partners to have opposite configuration. This can be clearly seen from the drawings (18) and (19).

It was reported⁸ that when an optically active sample of the acetal (20) was subjected to the conditions of rearrangement, the 3-benzyl-3,4-dihydroisoquinolinium salt (21) formed is optically active. This, it was suggested, showed that the



(20)

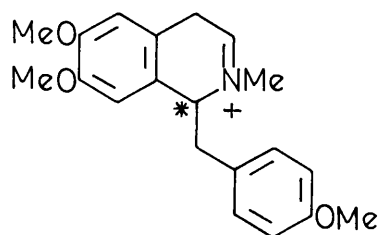


(21)

rearrangement of the 1-benzyl-1,2-dihydroisoquinoline derivative from (20) and of 1-benzyl-1,2-dihydroisoquinolines having a chiral centre at C₁ in general, occurs via transition state (18). The transition state (19) may be involved in the rearrangement of the racemic 1-benzyl-1,2-dihydroisoquinolines.

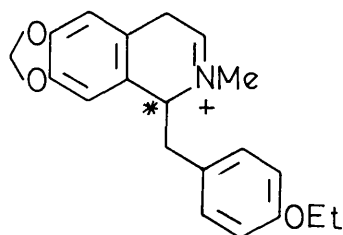
2. Objectives

The subject of this chapter is an investigation of the mechanism by rearrangement of an equimolar mixture of optically active (22) and (23) such that if (22) has the R configuration then (23) must have the S configuration or vice versa. It was reasoned that, by way of transition state (18), which requires both components



(22)

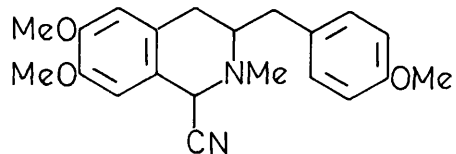
R or S



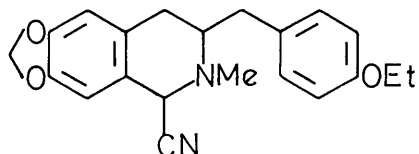
(23)

S or R

to be R or both S, compounds (24) and (27) would be the expected products. If transition state (19) is involved, however, molecules

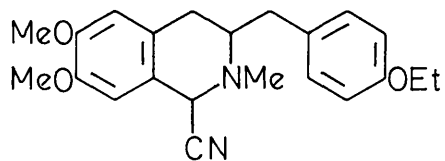


(24)

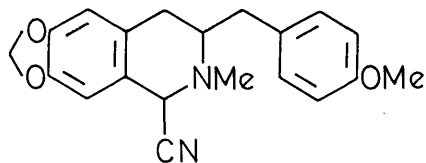


(27)

of opposite configuration can react together to form the rearrangement products (25) and (26). In this way it was hoped that the relative contributions of the two transition states (18) and (19) could be estimated by the product ratios.

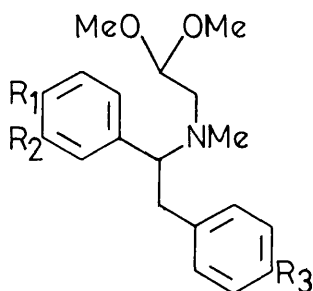


(25)



(26)

Quantitative mass spectrometry of the reaction product, it was hoped, would provide a suitable analytical method for the ψ -cyanide derivatives, authentic samples of which could be prepared from the corresponding benzylaminoacetals (28), (29), (30) and (31).



(28) $R_1 = R_2 = R_3 = \text{OMe}$

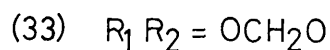
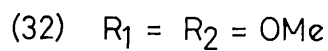
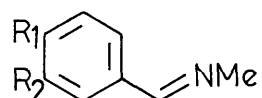
(29) $R_1 = R_2 = \text{OMe}, R_3 = \text{OEt}$

(30) $R_1 R_2 = \text{OCH}_2\text{O}, R_3 = \text{OMe}$

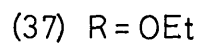
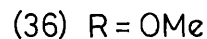
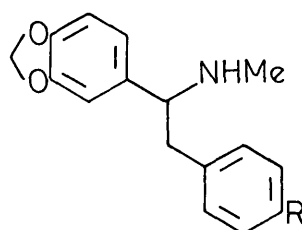
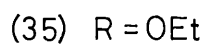
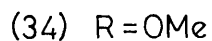
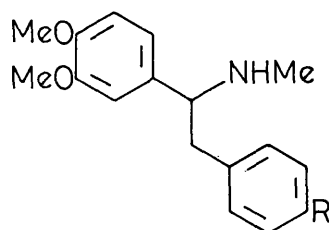
(31) $R_1 R_2 = \text{OCH}_2\text{O}, R_3 = \text{OEt}$

DISCUSSION1. Preparation of acetals

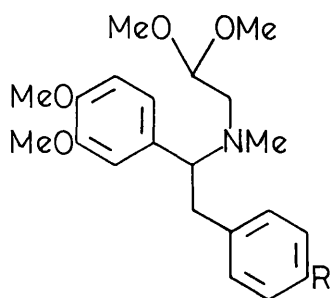
Reaction of the corresponding alkoxymagnesium grignard compounds in dry ether, with the Schiff's bases (32) and (33) afforded the amines (34), (35), (36), and (37). Elaboration



to the desired acetals (28) (29) (30) and (31) by reaction with

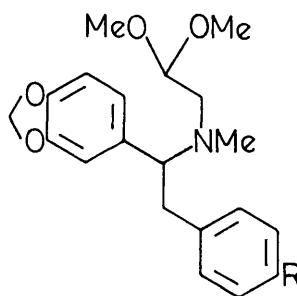


bromoacetal ($\text{BrCH}_2\text{CH}(\text{OMe})_2$) was investigated under a range of conditions (p223), and yields in excess of 90% of the alkylated materials were obtained by reaction of the amines with potassium



(28) R = OMe

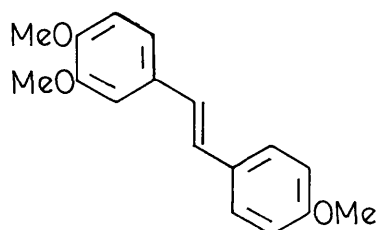
(29) R = OEt



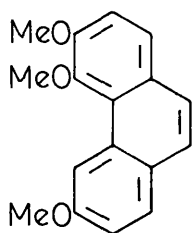
(30) R = OMe

(31) R = OEt

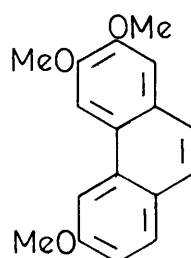
carbonate, dimethylformamide and bromoacetal at 100°. The reaction workup procedure involved extraction of the basic product into ice-cold normal sulphuric acid from ether solution. When the trimethoxy analogue (28) was prepared at the reflux temperature of the solvent an additional neutral product was isolated from the ether solution. On the basis of its ultraviolet spectrum which showed strong absorptions between 330 and 340nm, the trans stilbene structure (38) was assigned. After subjection to U.V. light¹⁴, its spectrum showed no absorptions above 284nm which is consistent with the phenanthrene structures (39a and b). Spectral and analytical data confirmed the stilbene (38)¹⁴ and a mass spectrum of (39) showed the molecular weight of 268, two less than that of (38).



(38)

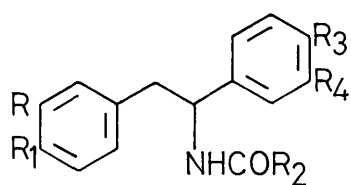


(39a)

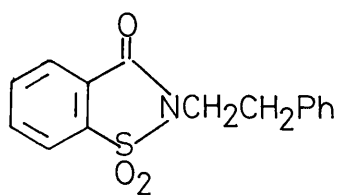


(39b)

A preparative method for trans stilbenes¹⁵ involves the treatment of amides of the type (40) with six normal hydrochloric



(40)

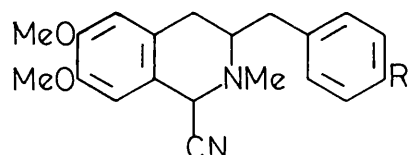


(41)

acid at reflux temperature. Deamination of (41) with hot potassium hydroxide has been reported to give styrene in a

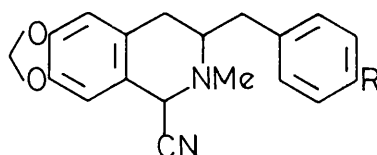
reasonable yield¹⁶. It is tempting to suggest therefore that the mild technique involving potassium carbonate and dimethyl formamide could provide a useful route to stilbenes, particularly so, in view of the aminonitrile route, to the required amines, described in chapter 2 of this thesis.

Treatment of the acetals (28), (29), (30) and (31) separately under the migration conditions of six normal hydrochloric acid gave the 3,4-dihydroisoquinoline- ψ -cyanides (24), (25), (26) and (27) respectively. The yields of migration products, however, were



(24) R = Me

(25) R = Et



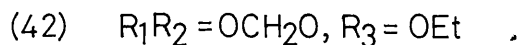
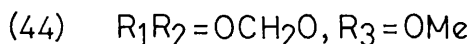
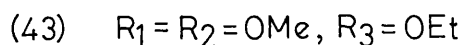
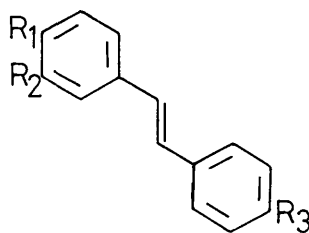
(26) R = Me

(27) R = Et

disappointing and much effort was directed at improvement. The results of these experiments are summarised in table I. From reactions of 3 hours or less duration basic material was isolated, in addition to 3,4-dihydroquaternary products, which made the total recovery to about 70%. Unfortunately, despite considerable effort no isolable products could be obtained from the basic fraction. It was noted that acid insoluble tars were formed during the migration reactions, and more so with the two methylenedioxy compounds (30) and (31). The longer the reaction was continued

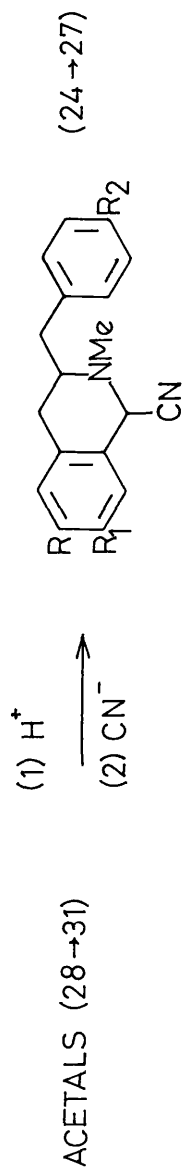
the more insoluble material seemed to be formed. In order to discern whether decomposition of the 3,4-dihydroisoquinolinium salt was accounting for these facts the ψ -cyanide (27) was treated with hydrochloric acid under the migration conditions. A yield of 95% unchanged starting material was recorded when worked up for ψ -cyanide. Examination of the products for phenolic compounds proved negative, which precludes breakdown of the methylenedioxy function.

A neutral product isolated from the insoluble tars from the migration reaction of (31) did however, clarify the situation a little. The crystalline compound was identified as the trans stilbene (42), and a closer re-examination of the non-basic material



from previous cyclisations afforded the three other stilbenes (38) (43) and (44). It was found that more of two methylenedioxy substituted compounds (42) and (44) were isolated than the 3,4-dimethoxy compounds (38) and (43). Although this difference was of the order of a factor of three or four, the amount of stilbene isolated never represented more than 10% of

Table I



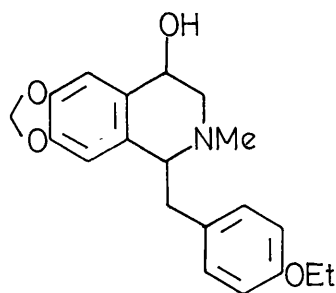
1) 6N HCl, sealed tube under N₂ for specified times, acetal conc. 1.5 m.moles/6mls acid

* acetal conc. 1.5 m.moles in 15 mls acid.

CONDITIONS PRODUCT	14 hrs. 100°	6hrs. 75°	3hrs. 100°	2hrs. 100°	1.5hr. 100°	1hr. 100°
(24)	50%	-	51%	-	-	32% 34%*
(25)	40%	-	30%	-	-	30% 33%*
(26)	< 5%	-	32%	13% 10%*	20%*	34% 32%*
(27)	< 5%	20%	12%	12% 11%*	24%*	32% 30%*

the reaction products. The residues, after isolation of the stilbenes, were retractable but showed U.V. spectra exhibiting absorptions which could be assignable to those structures.

The formation of stilbenes shows that there is an elimination reaction in competition with acetal cyclisation, a fact which has not been reported previously. The migration reactions were carried out in sealed vessels under nitrogen, in order that reagent concentrations remain constant and the possibility of oxygen induced elimination reactions⁹ are minimised. To show that the conditions employed were not excessive by comparison with some reported C₁ to C₃ migrations of this type a reaction was carried out using six normal hydrochloric acid at 100° in an unsealed vessel. The yield of migration product (24) formed under these conditions was 45%. A further experiment involved, hopefully, the prior formation of the 4-hydroxy derivative (45) by treatment

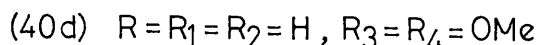
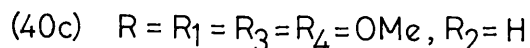
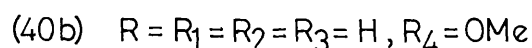
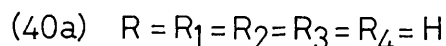
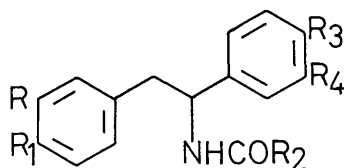


(45)

of the acetal (31) with six normal acid at 35°. Subsequent dilution of the acid to a strength of two normal, and treatment on a steam bath afforded less than 10% of the migration product (27).

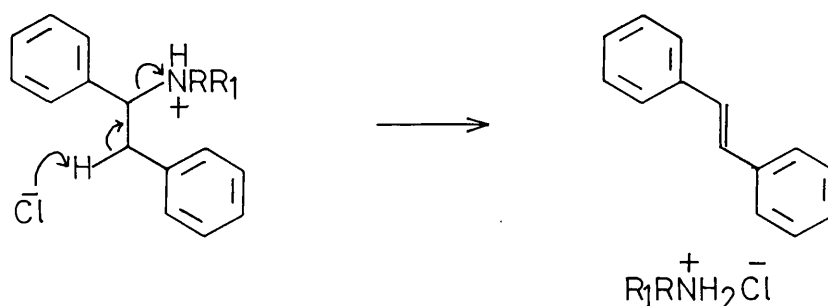
From the results presented thus far it seems likely that the stilbene or some unidentified reaction product either reacts with the 3,4-dihydroisoquinolinium salt or renders its isolation procedure less rewarding. It also appears, from the yields of migration products and the yields of stilbenes isolated that the methylenedioxy function is less nucleophilic than the two methoxy groups.

The formation of stilbenes¹⁵ discussed earlier p 199 suggests that amides of the type (40) undergo an E₂ type elimination in



hydrochloric acid. The authors demonstrate that alkoxy groups on the ring enhance this elimination dramatically, and that where no stilbene is isolated the product is amine hydrochloride. It seems, from isolation of stilbenes from the migration reactions,

that such stereospecific elimination reactions might well occur via the amine rather than the amide. To support this suggestion, the amides (40a) and (40b) are reported to give no stilbene. The methoxy compounds (40c) and (40d), which might be expected to afford a good yield of elimination product, also give none. This the author feels is a reflection of the stability of the formylamides to acid-catalysed hydrolysis to the amines. Mechanistically a trans E₂ elimination reaction of the amide would be less favoured than that of an amine in which the N-protonation acts as a driving force for the reaction (scheme 5).

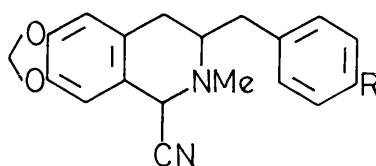
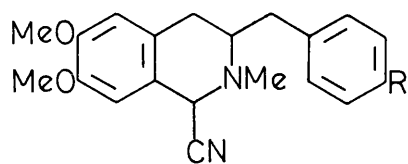


Scheme 5

2. Mixed Migration of racemic acetals

The limiting factor in the method so far is considered to be the generation of the 1-benzyl-1,2-dihydroisoquinolines from the acetals. However, the alternative approach to optically active 1-benzyl-1,2-dihydroisoquinolines involves the resolution of the base, through salts with optically active acids. This has been shown¹⁷ to cause disproportionation only. Consequently the chosen

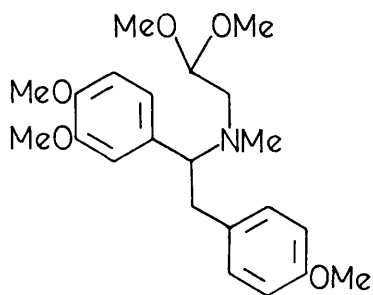
acetals (28)(29)(30) and (31) were treated with six normal hydrochloric acid for one hour at 100° , sealed under nitrogen. Under these conditions yields of the four migration products isolated were between 25 and 30%. The mass spectra of the four ψ -cyanide derivatives (24), (25), (26) and (27) obtained at low electron voltage, each shows a base peak corresponding to $M^{+}-HCN$



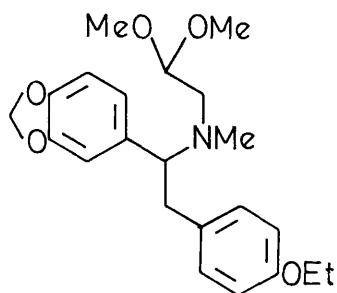
- (24) R=OMe ($325:M^{+}-HCN$) (26) R=OMe ($309:M^{+}-HCN$)
 (25) R=OEt ($339:M^{+}-HCN$) (27) R=OEt ($323:M^{+}-HCN$)

(values illustrated above). Standard mixtures of these four derivatives show mass spectra, under the same conditions, which are a combination of the four ψ -cyanides. In this way a method was developed to measure the product ratio in a mixture of the four possible migration products.

To test complete intermolecularity of cross migration, an equimolar mixture of racemic (28) and (31) was subjected to the standard acid conditions and the mass spectrum of the ψ -cyanide of the product showed a 1:1:1:1 mixture of (24):(25):(26):(27). An attempt to identify all four products by T.L.C.

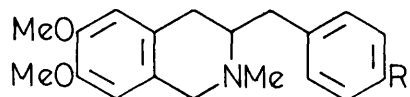


(28)

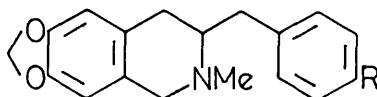


(31)

failed, but reaction of the product with sodium borohydride in ethanol afforded a mixture of the 3-benzyl-1,2,3,4-tetrahydroisoquinolines (46),(47),(48) and (49). T.L.C. of this mixture



(46) R = OMe



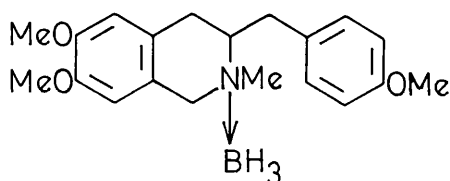
(48) R = OMe

(47) R = OEt

(49) R = OEt

showed four spots, identical by R.F. values, with samples of the tetrahydroderivatives prepared in the same way from the ψ -cyanide

compounds (24), (25), (26) and (27). Evidence for the formation of the N-borane (50)¹⁸ (M.S. and I.R.) from the reduction with

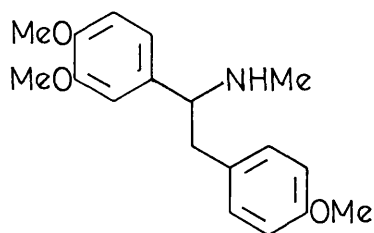


(50)

sodium borohydride prompted an acid treatment in the workup of the 3-benzyl-1,2,3,4-tetrahydroisoquinolines.

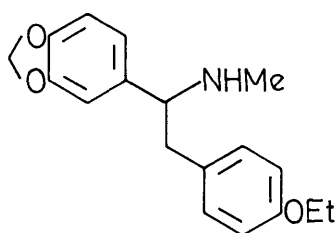
3. Optical resolutions.

Resolution of the acetals (28) and (31) with the (+) and (-) forms of dibenzoyltartaric acid proved to be impossible. However, after considerable difficulty, the optically active amines (51) and (52) were prepared by repeated crystallisations of the



(51)

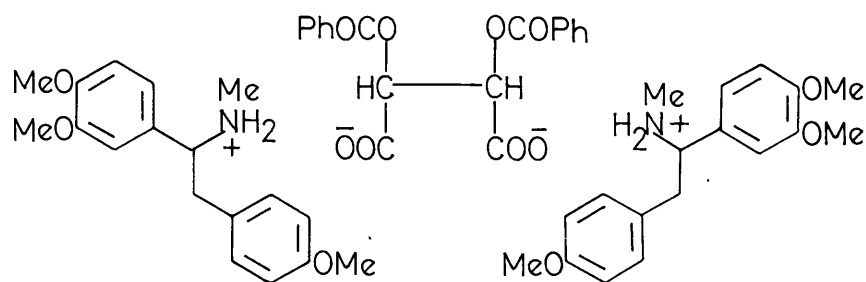
$$[\alpha]_D^{20} + 88.5^\circ$$



(52)

$$[\alpha]_D^{20} - 98^\circ$$

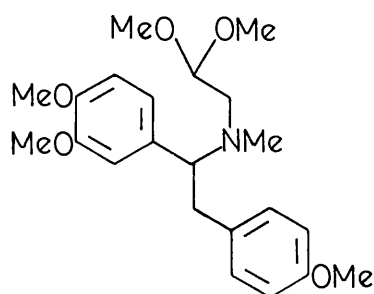
appropriate diastereomeric di-salts (53), formed by reaction of 2:1 molar ratio of racemic amine to optically active acid in



(53a)

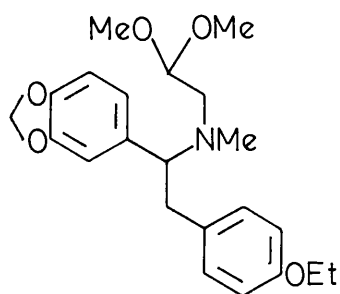
ethanol. The constitution, as disalts, was shown by N.M.R. elemental analysis and quantitative regeneration of the amine from a weighed sample of the salt.

Conversion of the optically active amines (51) and (52) to the corresponding acetals (54) and (55) proceeded smoothly in the



(54)

$$[\alpha]_D^{20} + 95^\circ$$

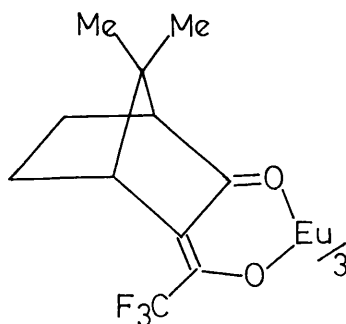


(55)

$$[\alpha]_D^{20} - 102^\circ$$

normal manner, and optical activity was retained. It was also shown that the optically active amine (51), when subjected to the alkylation conditions without bromoacetal, was recovered with the same specific optical rotation.

Although the diastereomeric salts of the amines (51) and (52) were recrystallised until the liberated base showed constant optical rotation, it was hoped that a measure of optical purity could be obtained by N.M.R. studies, making use of the chiral shift reagent tris-3-(trifluoromethylhydroxymethylene)-d-camphorato europium III (56)^{19a,b}. Such studies have been used successfully with aromatic

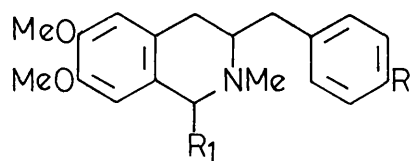
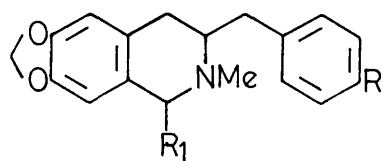


(56)

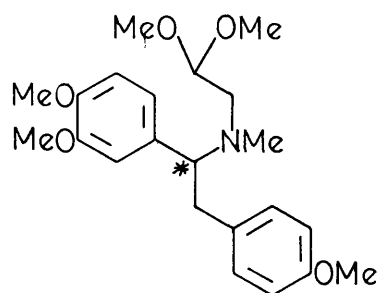
amines^{20a,b}, but from spectra obtained with the racemic and optically active amines, and acetals no measure of optical purity could be obtained.

4. Crossed migration of optically active acetals.

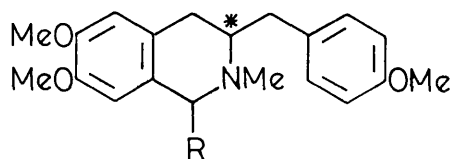
An equimolar mixture of the optically active (54) and (55) was subjected to the migration conditions and a 30% yield of ψ -cyanide derivatives isolated. The mass spectrum of the product showed the presence of (24):(25):(26):(27) in an approximately 1:1:1:1 ratio.

(24) R = OMe , R₁ = CN(25) R = OEt , R₁ = CN(46) R = OMe , R₁ = H(47) R = OEt , R₁ = H(26) R = OMe , R₁ = CN(27) R = OEt , R₁ = CN(48) R = OMe , R₁ = H(49) R = OEt , R₁ = H

Conversion to the 1,2,3,4-tetrahydroderivatives (46), (47), (48) and (49) was achieved in the normal manner. T.L.C. of the mixture confirmed the presence of all four products. An attempt to isolate each of them by chromatography in order to measure their optical rotations was unsuccessful. Optical retention was however, demonstrated when (54) was treated under the conditions of migration.



(54)



(57a) R = H

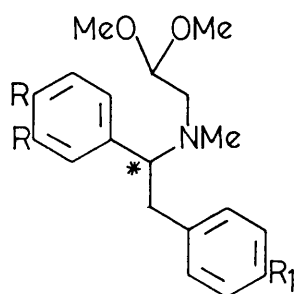
(57b) R = CN

The product was isolated as its ψ -cyanide derivative (57b) which when reacted with sodium borohydride gave the tetrahydro compound (57a). This had a specific rotation of $+76^{\circ}$ which was not altered by treatment with acid for up to ten hours. It seems likely, therefore, that considerable retention of optical activity is achieved under migration conditions. It proved impossible to measure the degree of retention as attempts to recrystallise (57a) as a dibenzoyl tartrate from either +D.B.T.A. or -D.B.T.A., resulted in failure.

The absolute configuration of the acetal (54) and the 3-benzyl derivative (57a) have not yet been deduced but it is hoped that optical rotatory dispersion or circular dichroism studies might realise this aim.

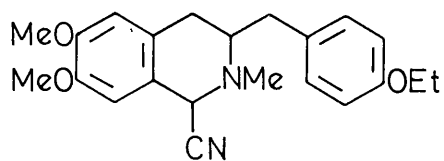
Conclusions

The rather low yields of migration products (approx. 30%) from the model compounds chosen for this study do not affect the interpretation of results in terms of reaction mechanism. It seems clear that a transition state such as (19), which requires both molecules to be of opposite configuration at C_1 , must have been involved in the formation of (25) and (26) from mixed migration reaction of the optically active acetals (54) and (55).

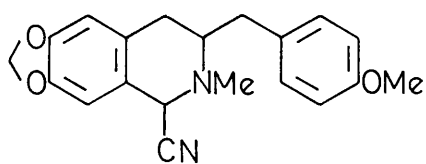


(54) $R=OMe$, $R_1=OMe$

(55) $RR=OCH_2O$, $R_1=OEt$

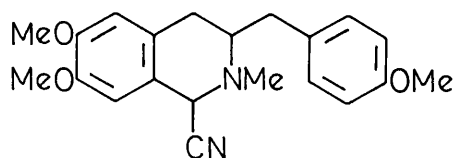


(25)

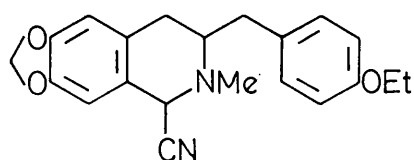


(26)

Transition state (18) which requires both components to be R or both S, can only explain the formation of (24) and (27).



(24)



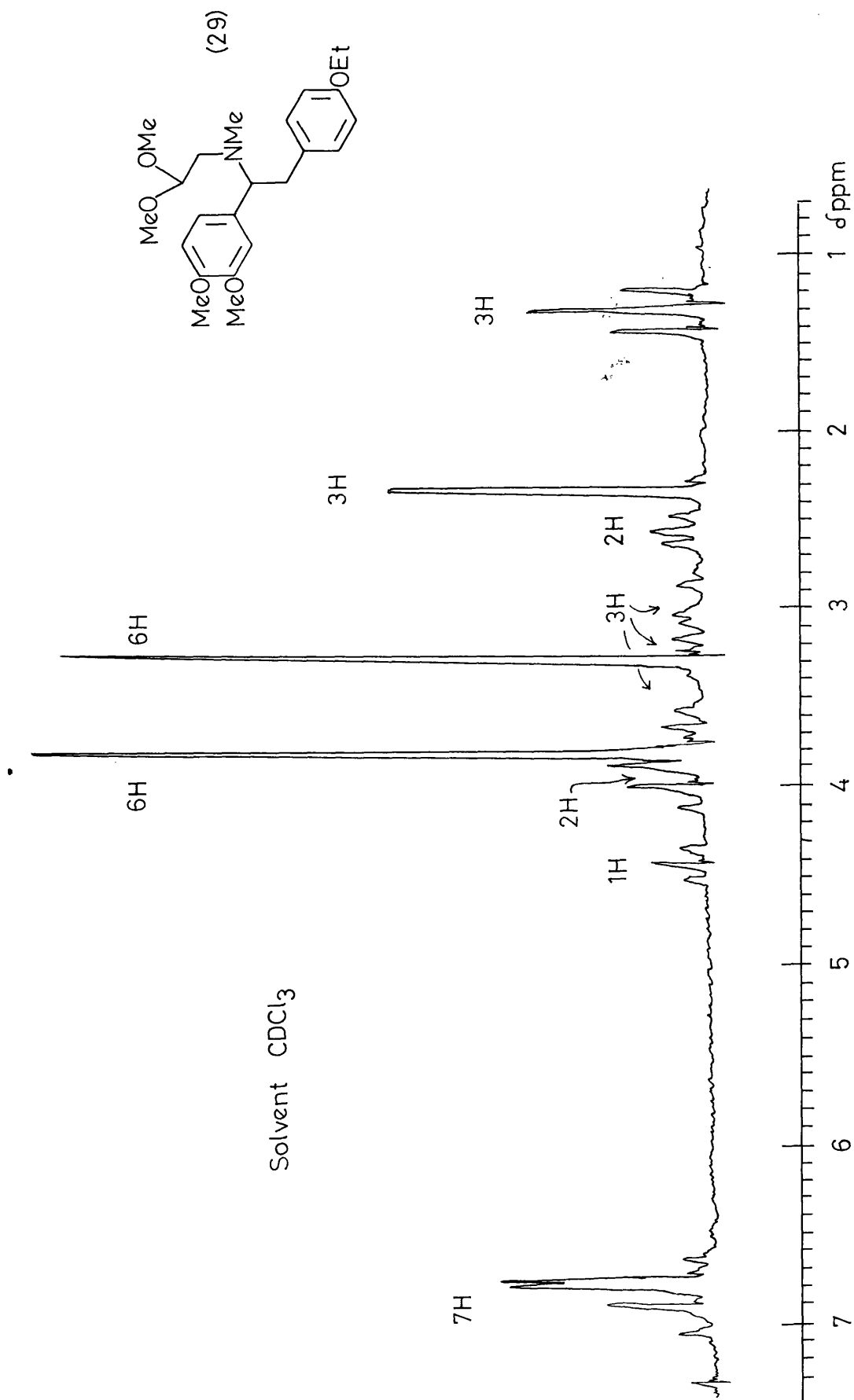
(27)

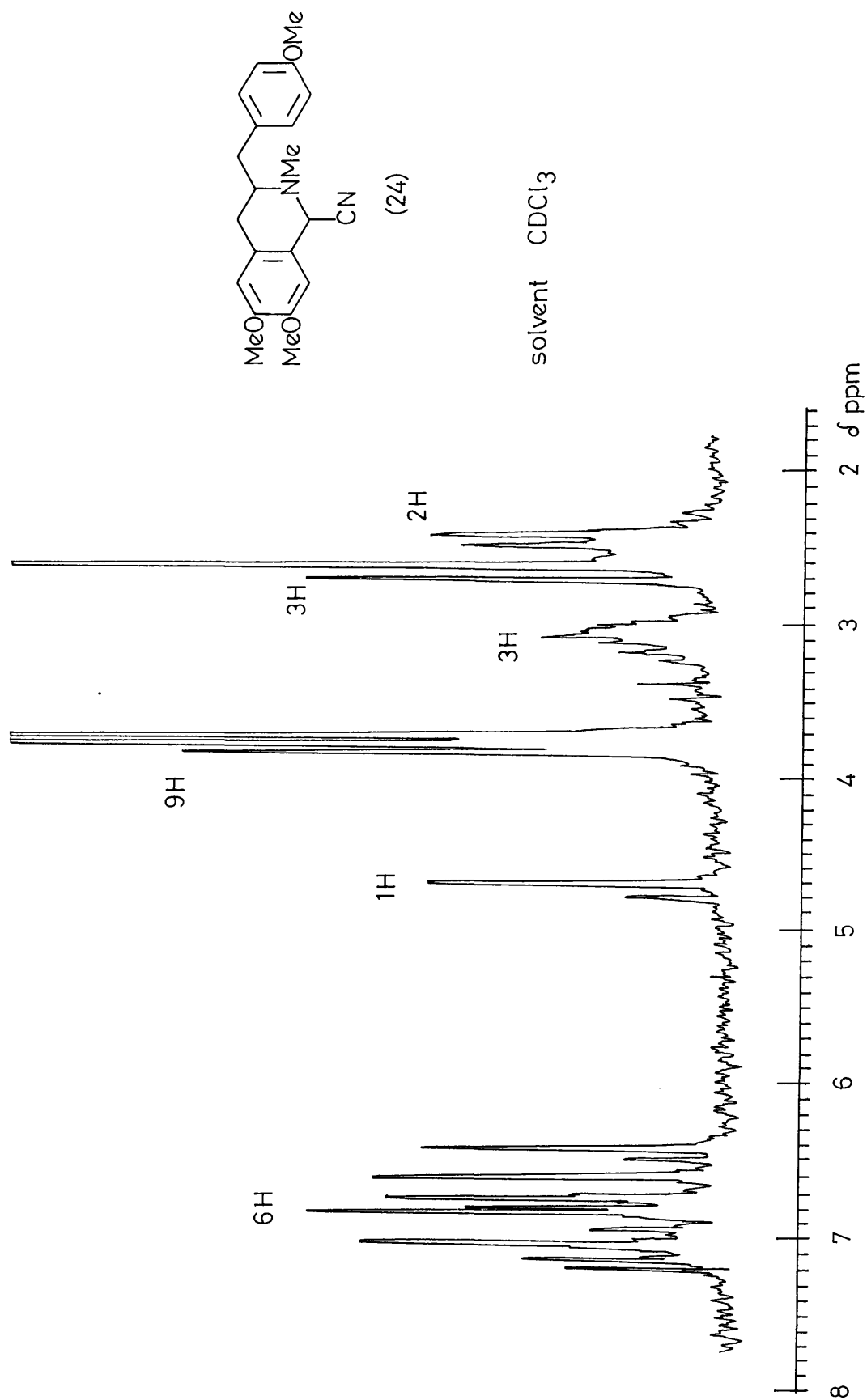
As mixed migration of the racemic acetals afforded the same ratio of products it seems likely that the energy differences between the two transition states (18) and (19) is not significant.

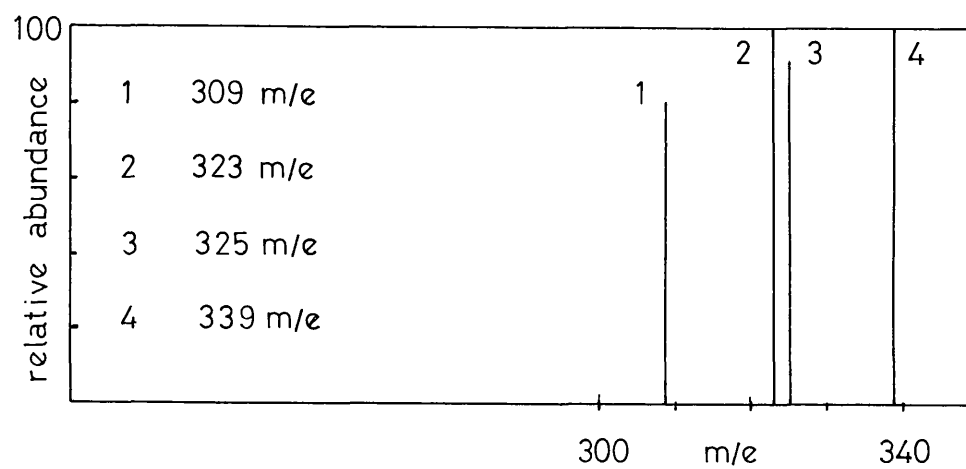
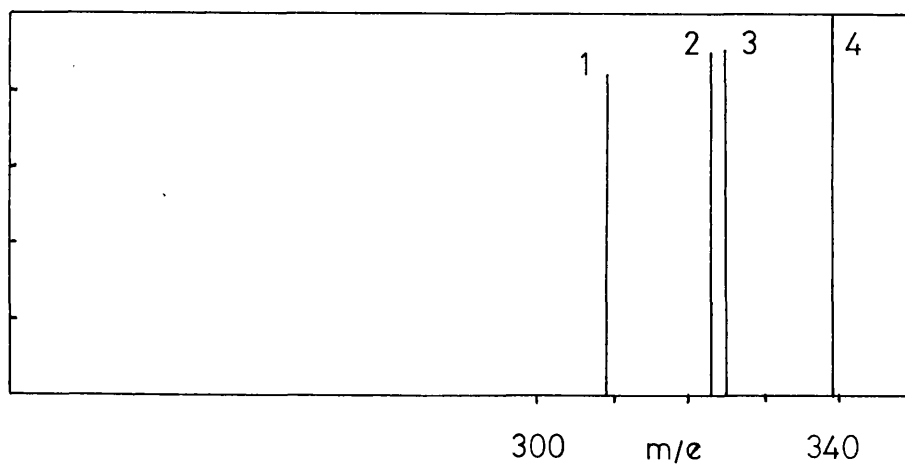
A limitation of the applied mass spectrometric technique was that, at best, a difference of $\pm 10\%$ on the peak heights was observed between two measurements of the same sample (see spectra). Consequently no estimation of the energy difference between the two transition states was possible.

This comparative mass spectrometric technique⁹ has not been widely reported but could, the author feels be a useful technique if instrument conditions are carefully reproduced and the compounds being studied have similar volatilities.

6. Spectra

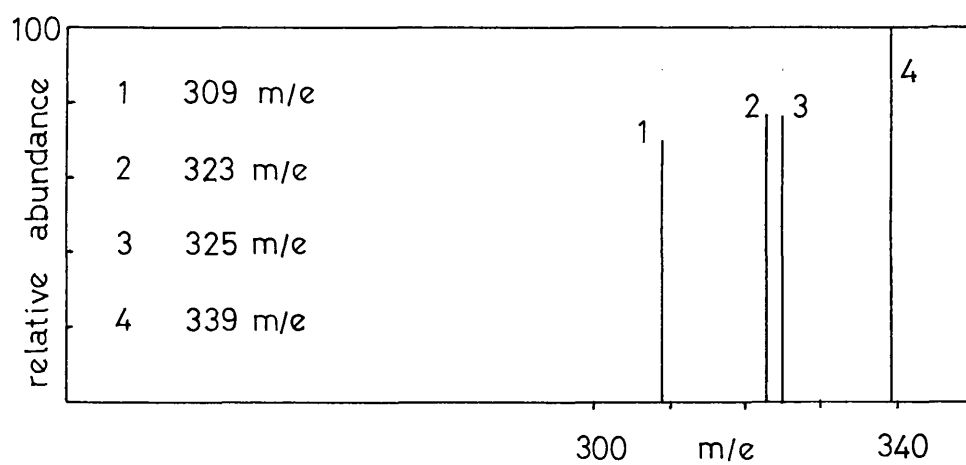
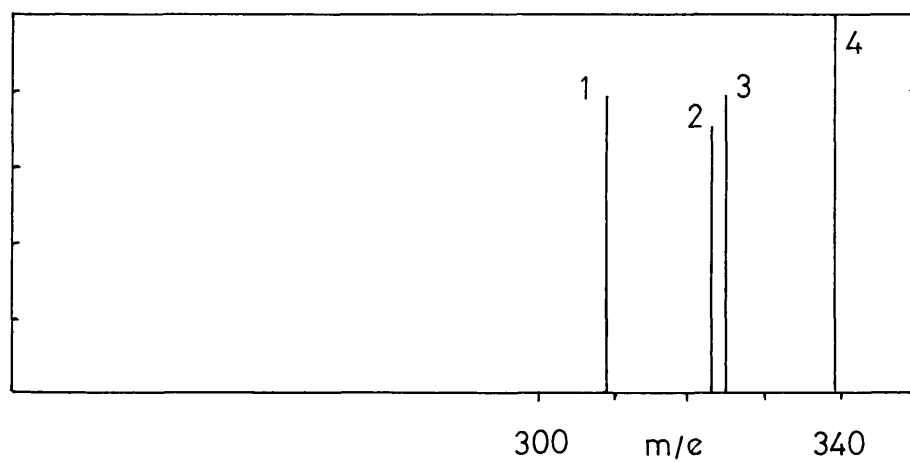






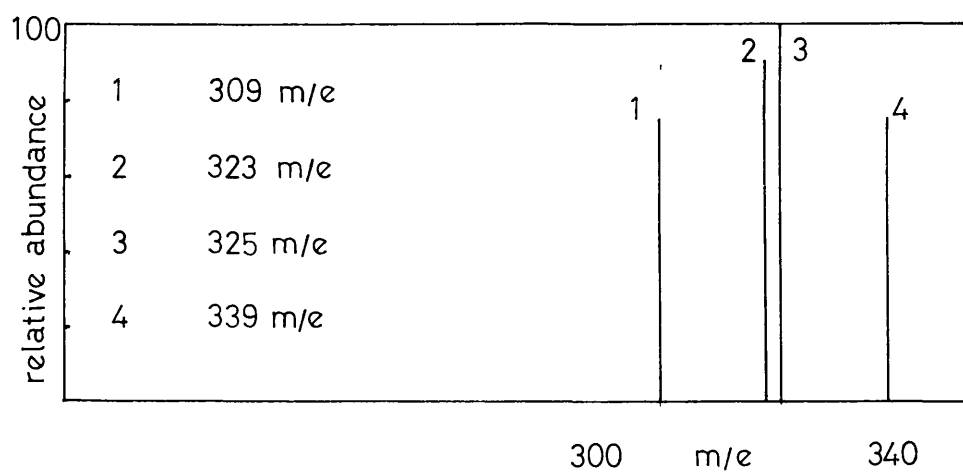
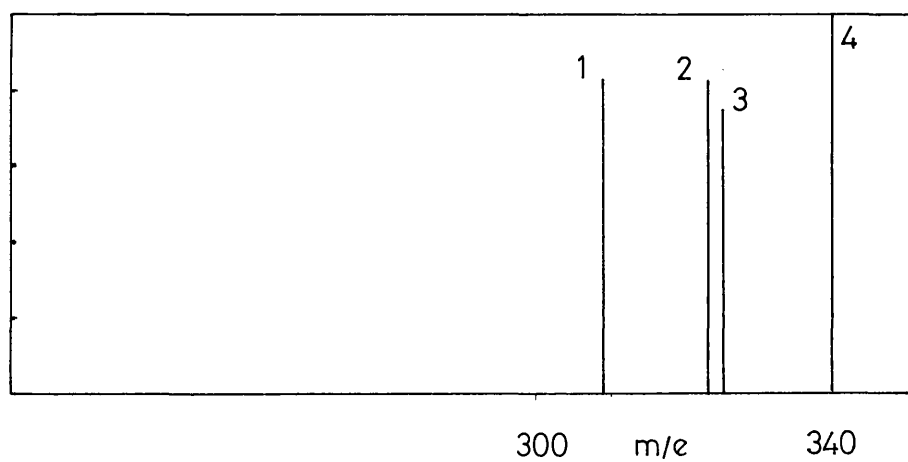
LOW ELECTRON VOLTAGE MASS SPECTRA OF TWO
STANDARD MIXTURES OF THE FOUR ψ -CYANIDES
(24-27) IN A 1:1:1:1 MOLAR RATIO

217a



LOW E.V. MASS SPECTRA OF ψ -CYANIDE MIXTURES
FROM TWO MIXED MIGRATIONS OF THE OPTICALLY
ACTIVE ACETALS (54) AND (55)

217b



LOW E.V. MASS SPECTRA OF ψ -CYANIDE MIXTURES

FROM TWO MIXED MIGRATIONS OF THE RACEMIC

ACETALS (28) AND (31)

7. Experimental

The Racemic amines (34) (35) (36) and (37) were prepared by the standard technique⁹ and purified (34), by vacuum distillation, and (35) (36) and (37) by crystallisation of the hydrochloride salts.

N-Methyl-N-[α -(4-methoxybenzyl)-3',4'-dimethoxybenzyl]amine (34),
 m.p. 63-5° (EtOH), N.M.R. (CDCl₃) 7.3-6.6 complex [7] (Aromatic H)
 3.85 s [6] (2 x ArOCH₃), 3.75 s [3] (ArOCH₃), 3.54 t [1] J=6Hz
 (Ar-CH₂-CH₂-Ar), 2.85 d [2] J=6 Hz (ArCH₂-CH-CH₂), 2.23 s [3] (N-CH₃),
 1.9 broad s [1] (NH, removed by D₂O); ν_{\max} 3315, 2790, 1614, 1517,
 1253, 1176, 1025; λ_{\max} (ϵ) 228 (20,800), 279 (4780); mass m/e
 301 (M⁺) (< 1%), 180 [100%], metastable at 107.4. (Found: C, 71.6;
 H, 7.6; N, 4.7. C₁₈H₂₃NO₃ requires: C, 71.7; H, 7.7; N, 4.7%).

N-methyl-N-[α -(4-ethoxybenzyl)-3',4'-dimethoxybenzyl]amine (35).
 m.p. 89° (EtOH), N.M.R. (CDCl₃) 7.2-6.7 complex [7] (Aromatic H),
 4.01 q [2] J=7Hz (OCH₂CH₃), 3.88 s [6] (2 x ArOCH₃), 3.7 multiplet
 [1](ArCH₂-CH₂-Ar), 2.86 d [2] J=7 Hz (Ar-CH₂-CH), 2.25 s [3] (N-CH₃),
 1.41 t [3] J=7 Hz (OCH₂CH₃), 1.5 broad [1] (NH, removed by D₂O);
 ν_{\max} 3300, 2790, 1610, 1510, 1248, 1130, 1031; λ_{\max} (ϵ) 230 (18,000),
 280 (3,240); mass m/e 315 (M⁺) [1%], 314 [5%], 285 [6%], 180 [100%].
 (Found: C, 72.5; H, 8.1; N, 4.3. C₁₉H₂₅NO₃ requires: C, 72.4;
 H, 8.0; N, 4.4%).

N-methyl-N-[α -(4-methoxybenzyl)-3',4'-methylenedioxybenzyl]amine (36),
 m.p. (HCl salt) 234-5° (EtOH), N.M.R. (free base) CDCl₃, 7.2-6.5
 complex [7] (aromatic H), 5.91 s [2] (O-CH₂-O), 3.75 s [3] (Ar-OCH₃),
 2.8 d [2] J=6.5 Hz (Ar-CH₂-CH-Ar), 3.55 d [1] J=6.5 Hz (Ar-CH₂-CH-Ar),
 2.18 s [3] (N-CH₃), 1.78 s [1] (N-H, removed by D₂O); ν_{\max} (free
 base) 3320 w, 2790, 1611, 1512, 1485, 1250, 1178, 1040; λ_{\max} (ϵ)

228 (11,560), 286 (4800); mass m/e (HCl salt), 285 ($M^+ - HCl$) [1%], 255 [3%], 164 [100%]. (Found: C, 63.6; H, 6.2; N, 4.2; Cl, 10.7. $C_{17}H_{19}NO_3HCl$ requires: C, 63.4; H, 6.2; N, 4.4; Cl, 11.0%).

N-Methyl-N-[α -(4-ethoxybenzyl)-3',4'-methylenedioxybenzyl amine (37).

m.p. (HCl salt) $235-6^\circ$ (EtOH), m.p. (free base) $63-4^\circ$, N.M.R. ($CDCl_3$) 7.0-6.6 complex [7] (aromatic H), 5.87 s [2] ($O-CH_2-O$), 3.92 q [2] $J=7$ Hz (OCH_2CH_3), 3.46 t [1] $J=6$ Hz ($Ar-CH-CH_2Ar$), 2.8-2.5 complex [2] ($ArCHCH_2-Ar$), 2.15 s [3] ($N-CH_3$), 1.36 t [3] $J=7$ Hz (OCH_2CH_3); ν_{max} (free base) 3300 w, 2790, 1609, 1510 1238, 1175, 1040; λ_{max} (ϵ) 228 (12,300), 285 (4,900); mass m/e 299 ($M^+ - HCl$) [5%], 269 [6%], 164 [100%]. (Found: C, 64.5; H, 6.6; N, 4.1; Cl, 10.4. $C_{18}H_{21}NO_3HCl$ requires: C, 64.4; H, 6.6; N, 4.2; Cl, 10.6%).

Alkylation of amines (34), (35), (36) and (37) with bromoacetal

Bromoacetal (3.0g) was added portionwise over 24 hr to the corresponding amine (1.2g) and K_2CO_3 (0.6g) in dry D.M.F. (20ml) at 100° . The reaction was maintained under N_2 for a further 24hr, cooled and quenched with H_2O (150ml), then extracted into C_6H_6 (4 x 50ml). The combined organic phase was washed with H_2O (5 x 20ml), and evaporated in vacuo to afford a yellow gum which was dissolved in ether and extracted into ice-cold 2N H_2SO_4 (3 x 15ml). Basification of the acid extracts with $NaHCO_3$ and extraction into ether (3 x 25ml) afforded a pale yellow soln which was dried ($MgSO_4$) and evaporated to afford the acetal (90-95%) as an oil.

N-Methyl-N-[α -(4-methoxybenzyl)-3',4'-dimethoxyl]aminoacetaldehyde dimethylacetal (28) N.M.R. (CDCl_3) 7.15-6.65 complex [7] (aromatic H) 4.44 t [1] $J=5$ Hz ($\text{CH}_2\text{-CH}(\text{OMe})_2$), 3.84 s [6] ($2 \times \text{ArOCH}_3$), 3.72 s [3] (Ar-OCH_3), 3.31 s [6] ($\text{CH-(OCH}_3)_2$), 3.9-2.4 complex [5] (aliphatic H) 2.36 s [3] (N-CH_3); ν_{max} (CHCl_3) 1595, 1493, 1240, 1023, 1008; λ_{max} (ξ) 227 (18,300), 279 (4,500); mass m/e 389 (M^+) [$<1\%$], 358 [6%], 271 [16%], 268 [60%], 252 [8%], 180 [20%], 87 [30%], 75 [17%], 47 [40%]. M^+-1 388.2127 $\text{C}_{22}\text{H}_{30}\text{NO}_5$ requires 388.2124.

N-Methyl-N-[α -(4-ethoxybenzyl)-3',4'-dimethoxybenzyl]aminoacetaldehyde dimethylacetal (29) N.M.R. (CDCl_3), 7.1-6.6 complex [7] (aromatic H, 4.43 t [1] $J=5$ Hz ($\text{CH}_2\text{-CH}(\text{OCH}_3)_2$), 3.95 q [2] $J=7$ Hz (OCH_2CH_3), 3.84 s [6] ($2 \times \text{Ar-OCH}_3$), 3.9-2.4 complex [5] (aliphatic H), 3.32 s [6] ($\text{CH}_2\text{CH}(\text{OCH}_3)_2$), 2.36 s [3] (N-CH_3), 1.34 t [3] (OCH_2CH_3); ν_{max} (CHCl_3) 1594, 1492, 1242, 1020, 1006; λ_{max} (ξ) 227 (17,500), 28 (5000); mass m/e 403 (M^+) [$<1\%$], 285 [18%], 268 [100%], 252 [10%], 180 [15%], 7.5 [12%].

N-Methyl-N-[α -(4-methoxybenzyl)-3',4'-methylenedioxybenzyl]aminoacetaldehyde dimethylacetal (30) N.M.R. (CDCl_3) 7.15-6.6 complex [7] (aromatic H), 5.92 s [2] ($\text{O-CH}_2\text{-O}$), 4.43 t [1] $J=5$ Hz ($\text{CH}_2\text{CH}(\text{OCH}_3)_2$), 3.75 s [3] (Ar-OCH_3), 3.8-2.65 complex [5] (aliphatic H), 3.33 s [6] ($\text{CH}_2\text{CH}(\text{OCH}_3)_2$), 2.31 s [3] (N-CH_3); ν_{max} (CHCl_3) 1613, 1510, 1240, 1040, 1025; λ_{max} (ξ) 227 (14,400), 286 (5,400).

N-Methyl-N-[α -(4-ethoxybenzyl)-3',4'-methylenedioxybenzyl] amino-acetaldehyde dimethylacetal (31). N.M.R. (CDCl_3) 7.15-6.6 complex [7] (aromatic H), 5.91 s [2] ($\text{O}-\text{CH}_2-\text{O}$), 4.41 t [1] $J=5$ Hz ($\text{CH}_2-\text{CH}-(\text{OCH}_3)_2$), 3.95 q [2] $J=7$ Hz (OCH_2CH_3), 3.8-2.6 complex [5] (aliphatic H), 3.32 s [6] ($\text{CH}_2-\text{CH}-(\text{OCH}_3)_2$), 2.31 s [3] ($\text{N}-\text{CH}_3$), 1.34 t [3] $J=7$ Hz (OCH_2CH_3); ν_{max} (CHCl_3) 1612, 1510, 1240, 1040, 1020; λ_{max} (ϵ) 227 (14,900), 286 (5400); mass m/e 387 (M^+) [$<1\%$], 252 [100%], 236 [10%], 164 [30%], 135 [9%], 75 [23%].

Isolation of Trans-3,4,4'-trimethoxystilbene (38). Alkylation of the amine (34), above, with bromoacetal, K_2CO_3 and D.M.F. at reflux temp. for 24 hr. afforded the required acetal (28) (56%) and from the non-basic fraction, the stilbene (38) (9%) as a white crystalline solid, m.p. 135° (MeOH) (lit. $133-5^\circ$ ¹⁵, N.M.R. (CDCl_3) 7.5-6.8 complex [9] (7 aromatic H + 2 olefinic H), 3.93 s, 3.89 s, 3.81 s [9] ($3 \times \text{Ar}-\text{OCH}_3$); ν_{max} 1610, 1518, 1265, 1140, 1025; λ_{max} (ϵ) 305 (12,400), 330 (16,000), 343 (11,400); mass m/e 270 (M^+) [100%]. (Found: C, 75.2, H, 6.6. $\text{C}_{17}\text{H}_{18}\text{O}_3$ requires C, 75.5; H, 6.7%). Irradiation of (38) with U.V. light afforded material, λ_{max} (ϵ) 230 (10,700), 257 (8,300), 284 (6,400); mass m/e 268 (M^+) [55%]. Considered to be phenanthrene (39).

Attempted alkylations of amine (34) with bromoacetal

CONDITIONS (under N ₂)		YIELD(BY NMR) OF ALKYLATED PRODUCT (28)
K ₂ CO ₃ /EtOH	48 hr reflux	20%
K ₂ CO ₃ /EtOH/Cubronze	48 hr reflux	20%
NaH/DMF	24 hr R.T.	0%
K ₂ CO ₃ /DMF	24 hr reflux	56% + 9% stilbene (38)
K ₂ CO ₃ /DMF	48 hr 100°	⋧ 90% yield

Resolution of amine (34).

The amine (34) (7.2g) and (-)-D.B.T.A. (4.7g) were dissolved in hot 95% EtOH (40ml) and stood at R.T. for 20 hr. Recrystallisation of the precipitated solid twice from EtOH afforded a white crystalline salt. m.p. 125-35°, N.M.R. (CDCl₃/D₂O) showed ratio of aromatic H:aliphatic H of 4:5, consistent with disalt (53a), ν_{max} (KBr) 2800-2200, 1710, 1260, 1030. (Found: C, 66.8; H, 6.5. C₅₄H₆₀N₂O₁₄ requires C, 67.5; H, 6.3%). Basification of the salt (285mg) with NaOH soln (10%, 10ml), and extraction into ether (3 x 25ml) afforded (+)-N-Methyl-N-[α -(4-methoxybenzyl)-3',4'-dimethoxybenzyl]amine (51) (173mg) $[\alpha]_{\text{D}}^{20} + 80^\circ$. The remainder of the disalt was recrystallised (8 times) until (51) showed a constant specific rotation of + 88.5°, m.p. 76°, N.M.R. (CDCl₃) as racemate (34).

Similarly (-)-N-Methyl-N-[α -(4-ethoxybenzyl)-3',4'-methylenedioxybenzyl]amine (52) was isolated from the racemic base (37) using (+)-D.B.T.A; m.p. 62°, $[\alpha]_{\text{D}}^{20} - 98^\circ$, N.M.R. (CDCl₃) as racemate (37).

Optically active acetals (54) and (55)

(+)-N-Methyl-N-[α -(4-methoxybenzyl)-3',4'-dimethoxybenzyl] aminoacetaldehyde dimethylacetal (54) was prepared from the amine (51) as a pale yellow oil (89%), $[\alpha]_{\text{D}}^{20} + 95^\circ$, by the method used to prepare its racemate (28). N.M.R. as racemate.

Similarly (-)-N-Methyl-N-[α -(4-ethoxybenzyl)-3',4'-dimethoxybenzyl] aminoacetaldehyde dimethylacetal (55) was prepared from the amine (52), $[\alpha]_{\text{D}}^{20} - 102^\circ$, N.M.R. as racemate.

Migration reactions : acid treatment of acetals.

The acetal (1m.mole) in 6N HCl (10ml, outgassed with N₂), was kept at 100° under N₂ in a stoppered tube for 1hr. The mixture was cooled, diluted with H₂O (10ml), washed with ether (3 x 10ml), basified (NaHCO₃) and extracted into CHCl₃ (4 x 10ml). Removal of the CHCl₃ in vacuo, afforded a gum which was leached with water at 35-40° (4 x 5ml). NaCN (25mg) was added to the NaHCO₃ soln and water leachings combined and the white precipitate extracted into ether (4 x 15ml). The ether extracts were washed with H₂O (3 x 10ml) dried (MgSO₄) and evaporated to give the ψ -cyanide derivatives (24), (25), (26) and (27) in yields (25-30%) see table I.

6,7-Dimethoxy-2-methyl-3-(4-methoxybenzyl)-1-cyano-1,2,3,4-tetrahydroisoquinoline (24) was obtained as a white crystalline solid on trituration from ether m.p. 138-40° N.M.R. (CDCl₃) 7.25-6.4 complex [6] (aromatic H), 4.83 s [0.2], 4.72 s [0.8] (C₁-H, diastereomers), 3.89s, 3.85s, 3.79s [12] (3 x ArOCH₃), 3.70-3.0 complex. [3] (aliphatic H), 2.75s, 2.63s [3] (N-CH₃, diastereomers), 2.5d [2] J = 7Hz (2 x C₄-H); ν_{\max} 2220, 1612, 1140; mass m/e (3ev) 325 (M⁺-HCN) [100%], 326 [25%], 231 [40%], 206 [60%]. (Found: C, 71.3; H, 6.9; N, 7.8. C₂₁H₂₄N₂O₃ requires: C, 71.6; H, 6.9; N, 8.0%).

6,7-Dimethoxy-2-methyl-3-(4-ethoxybenzyl)-1-cyano-1,2,3,4-tetrahydroisoquinoline (25), white crystalline solid on trituration from ether, m.p. 99°, N.M.R. (CDCl₃) 7.2-6.5 complex [6] (aromatic H),

4.85s [0.2] 4.75s [0.8] (C_1-H , diastereomers), 4.05 q [2] $J = 7\text{ Hz}$ (OCH_2CH_3), 3.85s, 3.80s [6] ($2 \times ArOCH_3$), 2.74s; 2.63s [3] ($N-CH_3$, diastereomers), 3.4-2.8 complex [3] (aliphatic H), 2.51 d [2] $J = 6.5\text{ Hz}$ ($2 \times C_4-H$), 1.4 t [3] $J = 7\text{ Hz}$ (OCH_2CH_3), ν_{\max} 2220, 1615, 1514, 1252, 1143, 1118, 799; mass m/e (3ev) 339 (M^+-HCN) [100%], 324 [20%], 231 [20%], 206 [100%]. (Found: C, 71.4; H, 7.2; N, 7.8. $C_{22}H_{26}N_2O_3$ requires: C, 71.2; H, 7.4; N, 7.9%).

6,7-Methylenedioxy-2-methyl-3-(4-methoxybenzyl)-1-cyano-1,2,3,4-tetrahydroisoquinoline (26), pale lemon crystals from ether, m.p. $94-5^\circ$ N.M.R. ($CDCl_3$) 7.3-6.4 complex [6] (aromatic H), 5.95s, 5.91s [2] ($O-CH_2-O$, diastereomers), 4.79s [0.2], 4.69s [0.8] (C_1-H , diastereomers), 3.8 s [3] ($ArOCH_3$), 3.3-2.4 complex [5] (aliphatic H), 2.72s, 2.62s [3] ($N-CH_3$, diastereomers); ν_{\max} 2220, 1615, 1516, 1247, 1040, 842 mass m/e (3ev) 309 (M^+-HCN) [100%], 310 [27%], 215 [30%]. (Found: C, 71.7; H, 5.8; N, 8.2. $C_{20}H_{20}N_2O_3$ requires: C, 71.4; H, 5.99; N, 8.3%).

6-7-Methylenedioxy-2-methyl-3-(4-ethoxybenzyl)-1-cyano-1,2,3,4-tetrahydroisoquinoline (27) offwhite solid on trituration from ether m.p. $90-4^\circ$, N.M.R. ($CDCl_3$) 7.3-6.45 complex [6] (aromatic H), 5.99s, 5.94 s [2] ($O-CH_2-O$, diastereomers), 4.81 s [0.2], 4.7 s [0.8] (C_1-H diastereomers), 4.05 q [2] $J = 7\text{ Hz}$ (OCH_2CH_3), 3.3-2.8 complex [3] (aliphatic H), 2.74 s, 2.62 s [3] ($N-CH_3$, diastereomers), 2.5d [2] $J = 6\text{ Hz}$ ($2 \times C_4-H$), 1.4 t [3] $J = 7\text{ Hz}$ (OCH_2CH_3); ν_{\max} 2220, 1515, 1042 mass m/e (3ev)

323 (M^+ -HCN) [100%], 324 [30%], 215 [90%]. (Found: C, 71.5; H, 6.7; N, 8.4. $C_{21}H_{22}N_2O_3$ requires: C, 72.0; H, 6.3; N, 8.0%).

Migration of (+)-N-methyl-N-[α -(4-methoxybenzyl)-3',4'-dimethoxybenzyl]aminoacetaldehyde dimethyl acetal (54)

The acetal (54) 580mg 6N HCl (15ml) treated under the described migration conditions afforded the 3-benzyl- ψ -cyanide derivative (57b) 168mg (31%). To this was added EtOH (10ml) and $NaBH_4$ (80mg) and the reaction heated under reflux for 1hr. The solvent was removed and H_2O (10ml) added and the product extracted into ether (3 x 10ml). The combined extracts were washed (H_2O), and extracted into 2N HCl (3 x 10ml). Basification of the acidic solution with NaOH (1N) followed by extraction into $CHCl_3$ (3 x 20ml) afforded the 6,7-dimethoxy-2-methyl-3-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (57a) as a pale yellow oil $[\alpha]_D^{21} + 76^\circ$ 129mg, 82% based on ψ -cyanide (57b). A repeat of this reaction using a fresh batch of the optically active acetal (54) afforded a 68% yield, $[\alpha]_D^{21} + 75^\circ$. N.M.R. ($CDCl_3$) 7.15 - 6.45 complex [6] (aromatic H), 3.85-3.70 complex [11] (3 x $ArOCH_3$ plus C_1-CH_2), 3.49 s [3] ($N-CH_3$), 3.4-2.35 complex [5] (C_4-CH_2 , $Ar-CH_2$ plus C_3-H); $\lambda_{max}(\xi)$ 288 (5600); mass m/e 327 (M^+) 206 [70%], 205 [20%]. Perchlorate salt (EtOH) (61%) m.p. 124-6° mass m/e 326 [2%], 205 [100%], 204 [90%].

Attempts to form diastereomeric salts of (57) with either (+) or (-) forms of D.B.T.A. resulted in failure. Although a solid derivative was formed with (-) D.B.T.A, all attempts at recrystallisation from EtOH, acetone, MeOH and ether gave only oils.

T.L.C. of ψ -cyanide and tetrahydro-3-benzyl derivatives

The ψ -cyanides (24, 25, 26 and 27) would not run by T.L.C. on either alumina or silica.

In the manner described above, 20mg of each of the ψ -cyanide derivatives were converted by NaBH_4 into the 3-benzyl-1,2,3,4-tetrahydroisoquinolines (46, 47, 48 and 49). With example (24) the product was at first not purified by extraction into 2N HCl, and T.L.C. on alumina (eluted with 4 x C_6H_6 and 2 x $\text{C}_6\text{H}_6/\text{CHCl}_3$ 7/1) showed two spots. Material at RF 0.9 was extracted from the alumina into CHCl_3 , ν_{max} 2333, 2294, mass m/e 341 (M^+) [8%] 340, 339, 220 [100%]. This evidence is consistent with the N-borane structure (50). The material at RF 0.8 was also extracted into CHCl_3 , ν_{max} showed no absorptions 2000-2600, mass m/e 327 (M^+) 206, 205 consistent with the desired racemic 6,7-dimethoxy-2-methyl-3-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (46).

Using this acid extraction, the tetrahydroisoquinolines (47), (48) and (49) were prepared and shown to possess no N-borane material. The T.L.C. characteristics of the four compounds were very similar with (46) and (47) running almost together RF 0.6, and (48) and (49) slightly faster at RF 0.65 (these figures were obtained using six elutions as described above).

Cross Migration Reactions

i. Racemic. The racemic acetals (28) (38.9mg, 0.1m.moles) and (31) (39.0mg, 0.1m.moles) were dissolved in CHCl_3 and the solvent removed under high vacuum. The mixture was treated with hot 6N HCl (2ml, outgassed with N_2) and kept at 100° under

N_2 in a stoppered tube for 1hr. Workup according to the procedure described on page 225 afforded a mixture of ψ -cyanide derivatives (18mg, 26%). A duplicate reaction gave (20.5mg, 29%) mass m/e 5ev 309, 323, 325, 339 (see spectral section).

A sample of the ψ -cyanide derivatives was treated with $NaBH_4$ in EtOH and extracted from ether into 2N HCl in the manner described before. T.L.C. over alumina confirmed the presence of the four 3-Benzyl-1,2,3,4-tetrahydroisoquinolines (46), (47), (48) and (49) by comparison with the samples prepared from the authenticated ψ -cyanide derivatives (24), (25), (26) and (27).

ii Optically active. The optically active acetals (54) (38.7mg, 0.1 m.moles) and (55) (38.9mg, 0.1 m.moles) were mixed and treated in the same way as above and a mixture of ψ -cyanides (17.5mg, 25%) and (20mg, 28.5% for repeat) were isolated; mass m/e 5ev 309, 323, 325 and 339 (see spectral section).

Also in an analogous manner to that described above the ψ -cyanide mixture was treated with $NaBH_4$ and the presence of all four derivatives (46) (47), (48) and (49) indicated by T.L.C. comparisons with samples obtained from authentic ψ -cyanide derivatives (24), (25), (26) and (27).

Isolation of stilbenes (38), (43), (44) and (42).

The acid insoluble material, which did not extract into the ether, from the migration reactions of the racemic acetals (28), (23), (30) and (31) was treated twice with charcoal and hot methanol. The charcoal was filtered and the red solutions

evaporated and the residues crystallised from MeOH. The solids were collected and again treated with charcoal prior to recrystallisations. This procedure was carried out on the 3hr 100°, migration reactions and the acid insoluble material from the methylenedioxy compounds (30) and (31) represents approximately 20-25% of the product whereas the trimethoxy compound (28) only 10%, and (29) approximately 15%. Trans-3,4,4'-trimethoxystilbene (38) (2%) was isolated, m.p. 135° (MeOH) same data as on page 222.

Trans-3,4-dimethoxy-4'-ethoxystilbene (43) (5%) m.p. 138-9°, N.M.R. (CDCl₃) 7.45-6.8 complex [9] (aromatic H, plus olefinic H), 3.92 s [3], 3.87 s [3] (2 x ArOCH₃), 4.04 q [2] J = 6.5 Hz (ArOCH₂CH₃), 1.40 t [3] J = 6.5 Hz (ArOCH₂CH₃); ν_{\max} 1516, 1249, 1136, 969; λ_{\max} (ξ) 294 (20,600), 305 (24,400), 320 (28,300), 332 (31,000), 345 (22,500) after exposure to UV λ_{\max} 258, 286, 300sh; mass m/e 284 (M⁺) [100%], 269 [19%], 255 [22%], metastables 254.5, 229. (Found: C, 75.7; H, 7.4. C₁₈H₂₀O₃ requires C, 76.0; H, 7.1%).

Trans-3,4-methylenedioxy-4'-methoxystilbene (44) (8%) m.p. 143-143.5, N.M.R. (CDCl₃) ν_{\max} 1513, 1257, 1180, 959, 935; λ_{\max} (ξ) 295 (20,000), 306 (20,600), 334 (30,100), 347 (21,000), after exposure to UV λ_{\max} 255, 295; mass m/e 254 (M⁺) [100%], 239 [23%], metastable 225.

Trans-3,4-methylenedioxy-4'-ethoxystilbene (42) (9-10%) m.p. 141-2° N.M.R. (CDCl₃) 7.48-6.75 complex [9] (aromatic H plus olefinic H), 5.95 s [2] (O-CH₂-O), 4.03 q [2] J = 6.5 Hz (ArOCH₂CH₃), 1.42 t [3] J = 6.5 Hz (ArOCH₂CH₃); λ_{\max} (ξ) 295 (23,200), 307 (24,100), 334 (31,700), 348 (23,200); mass m/e 268 (M⁺) [100%], 239 [12%], 238 [11%], metastables 213.2, 214.6. After exposure to UV, λ_{\max} 255, 289, 300sh.

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